Cutaneous lymphomas

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Lymphoma Def.

- malignancy of the immune cells
- characterized by an abnormal clonal proliferation of lymphocytes and related cell types
- most lymphomas begin in the lymph nodes

Classification of Lymphomas

- Hodgkin's Lymphomas
  - Lymph nodes
  - Skin changes in 30% of patients
  - Pruritus is a subjective symptom
  - Marker CD30 typical for malignant cells (Reed-Stemberg cells)
- non-Hodgkin's Lymphomas
  - T cell lymphomas of the skin mycosis fungoides, Sezary syndrome, pagetoid reticulosis
  - B cell lymphomas

Classification of Lymphomas

- Hodgkin's Lymphomas
- non-Hodgkin's Lymphomas

75-80%

- T cell lymphomas of the skin mycosis fungoides, Sezary syndrome, pagetoid reticulosis

20-25%

- B cell lymphomas

Primary cutaneous lymphomas

Table 1 WHO classification of cutaneous lymphomas (Blue book 2008).

Cutaneous T-cell and NK cell lymphomas	Cutaneous B-cell lymphomas
Mycosis fungoides (MF)	▸ Primary cutaneous follicular B-cell lymphoma (PCFCL) ▸ Primary cutaneous marginal zone B-cell lymphoma (PCMCL) ▸ Primary cutaneous diffuse large B-cell lymphoma – leg type (PCBLT) ▸ Primary cutaneous diffuse large cell B-cell lymphoma, other types ▸ Primary cutaneous intravascular large B-cell lymphoma
Mycosis fungoides variants and sub-types ▸ Folliculotropic MF ▸ Pagetoid reticulosis ▸ Granulomatous slack skin	
Sézary syndrome (SS)	
Adult T-cell leukemia/lymphoma	
Primary cutaneous CD30+ lymphoproliferative diseases ▸ Primary cutaneous anaplastic large-cell lymphoma (PCALCL) ▸ Lymphomatoid papulosis (LyP)	
Subcutaneous panniculitis-like T-cell lymphoma (SPTCL)	
Extranodal NK/T-cell lymphoma, nasal type	
Primary cutaneous γ/δ T-cell lymphoma ▸ Primary cutaneous aggressive epidermotropic CD8+ T-cell lymphoma (provisional) ▸ Primary cutaneous small/moderate-sized pleomorphic T-cell lymphoma (provisional)	
Peripheral T-cell lymphoma, not specified	

Hematological precursor neoplasms

CD4+, CD56+ hematodermic neoplasm (plasmacytoid dendritic cell neoplasm)

Table 41.1 The Classification of cutaneous lymphomas used in this chapter (based on the WHO–EORTC classification)

Cutaneous T-cell and NK-cell lymphomas

Mycosis fungoides and subtypes
- Folliculotropic mycosis fungoides
- Pagetoid reticulosis
- Granulomatous slack skin
- Hydroa vacciniforme-like lymphoma

Sézary syndrome
Adult T-cell leukemia/lymphoma
Primary cutaneous $CD30^+$ lymphoproliferative disorders
- Primary cutaneous anaplastic large cell lymphoma
- Lymphomatoid papulosis

Subcutaneous panniculitis-like T-cell lymphoma
Extranodal NK/T-cell lymphoma, nasal type
Primary cutaneous peripheral T-cell lymphoma, unspecified
- Primary cutaneous aggressive epidermotropic $CD8^+$ T-cell lymphoma (provisional)
- Cutaneous γ/δ T-cell lymphoma (provisional)
- Primary cutaneous $CD4^+$ small/medium pleomorphic T-cell lymphoma (provisional)

Cutaneous B-cell lymphomas

Primary cutaneous marginal zone B-cell lymphoma
Primary cutaneous follicle center cell lymphoma
Primary cutaneous diffuse large B-cell lymphoma, leg type
Primary cutaneous diffuse large B-cell lymphoma, other
- Intravascular large B-cell lymphoma
- Plasmablastic lymphoma
- T-cell/histiocyte-rich B-cell lymphoma
- Lymphomatoid granulomatosis

Precursor hematologic neoplasm

Blastic plasmacytoid dendritic cell neoplasm

Other T/NK-cell lymphomas that may involve the skin

Precursor T-lymphoblastic lymphoma/leukemia
T-cell prolymphocytic leukemia
Angioimmunoblastic T-cell lymphoma
Primary systemic anaplastic large cell lymphoma
Intravascular T- and NK-cell lymphoma
Aggressive NK-cell leukemia
Other T/NK-cell lymphomas and leukemias

Other B-cell lymphomas that may involve the skin

Precursor B-lymphoblastic leukemia/lymphoma
Chronic lymphocytic leukemia/small lymphocytic lymphoma
Mantle cell lymphoma
Primary effusion lymphoma
Lymphoplasmacytic lymphoma/Waldenström's macroglobulinemia
Burkitt and Burkitt-like lymphoma
Plasmacytoma and secondary myeloma

Other lymphomas

Hodgkin lymphoma

Cutaneous infiltrates of leukemias

Myeloid leukemias, myeloproliferative diseases and myelodysplastic syndromes

Lymphoid hyperplasia mimicking primary lymphoma

Lymphoid hyperplasia simulating B-cell lymphoma
Lymphomatoid drug reactions
Reactions resembling $CD30^+$ lymphoproliferative disorders
Pseudolymphomatous folliculitis
Jessner's lymphocytic infiltrate
Acral pseudolymphomatous angiokeratoma
Cutaneous $CD8^+$ T-cell infiltrates in HIV/AIDS

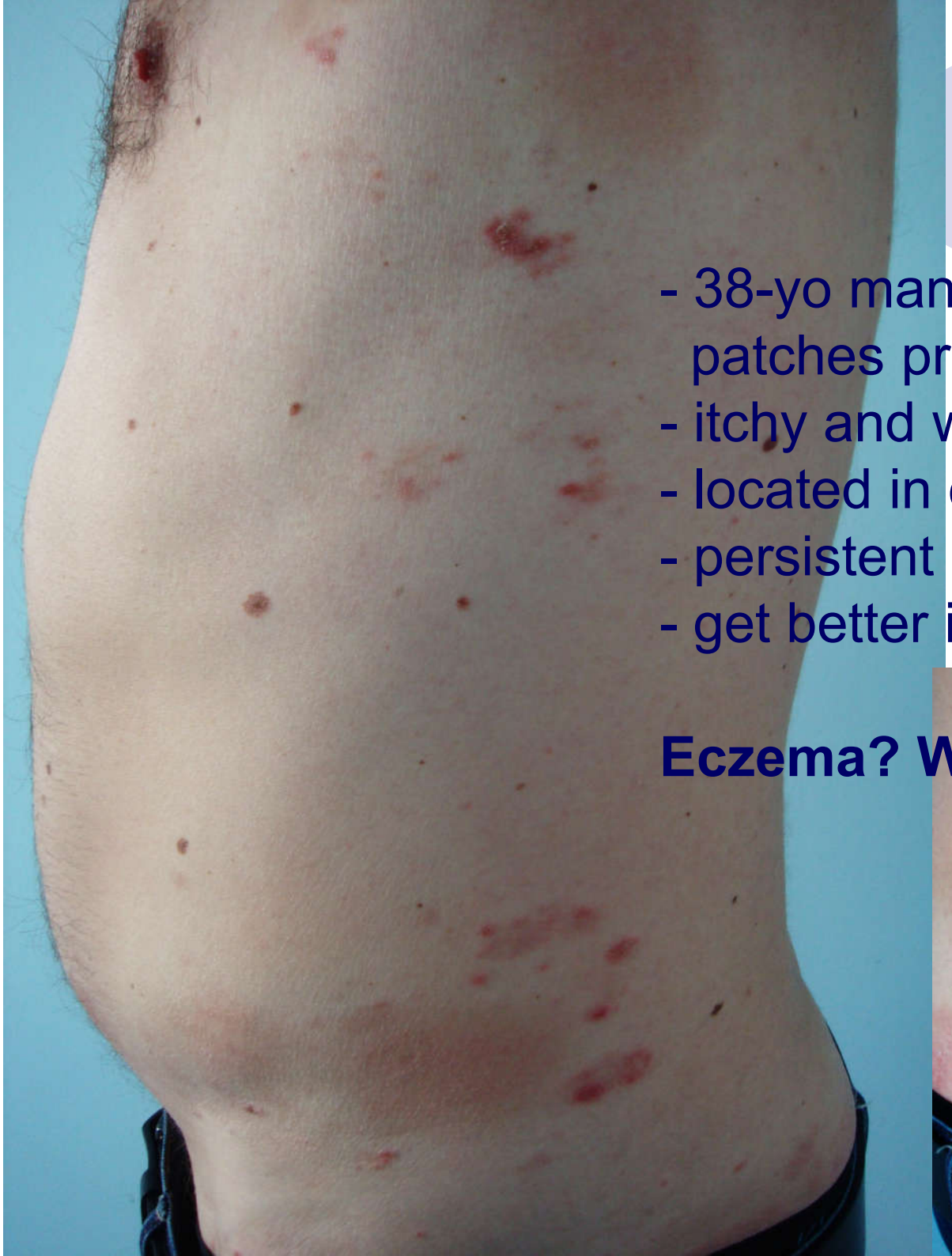
Cutaneous infiltrates in post-transplant lymphoproliferative disorders

Other lymphoproliferative disorders associated with immunosuppression

Methotrexate-associated lymphoproliferative disorders
Cutaneous infiltrates in HIV/AIDS

Miscellaneous

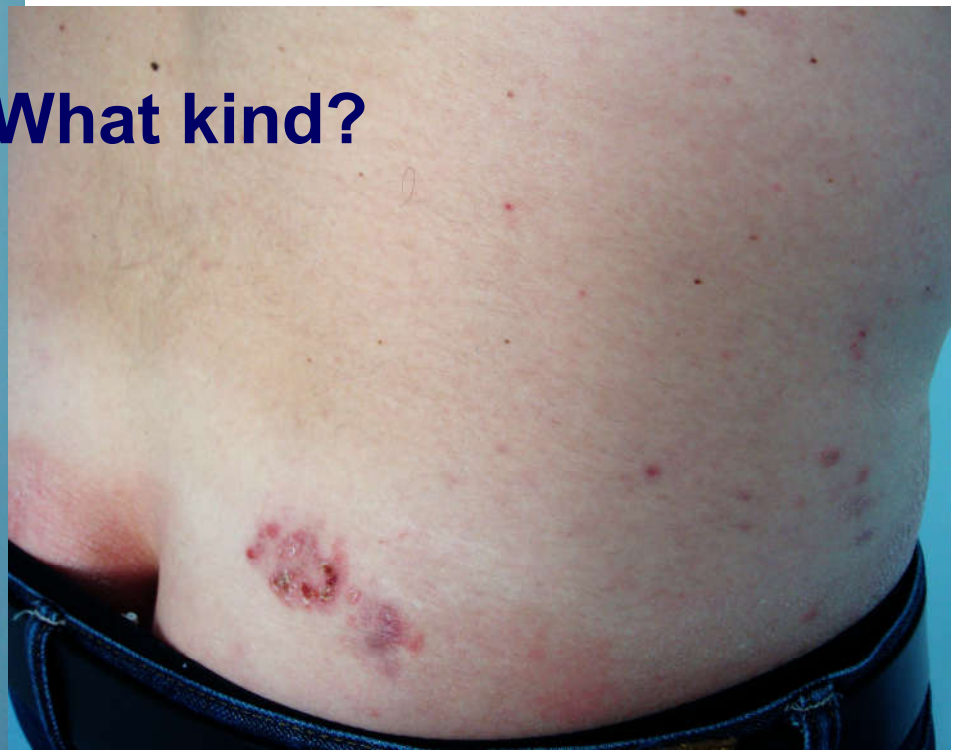
Extramedullary hematopoiesis



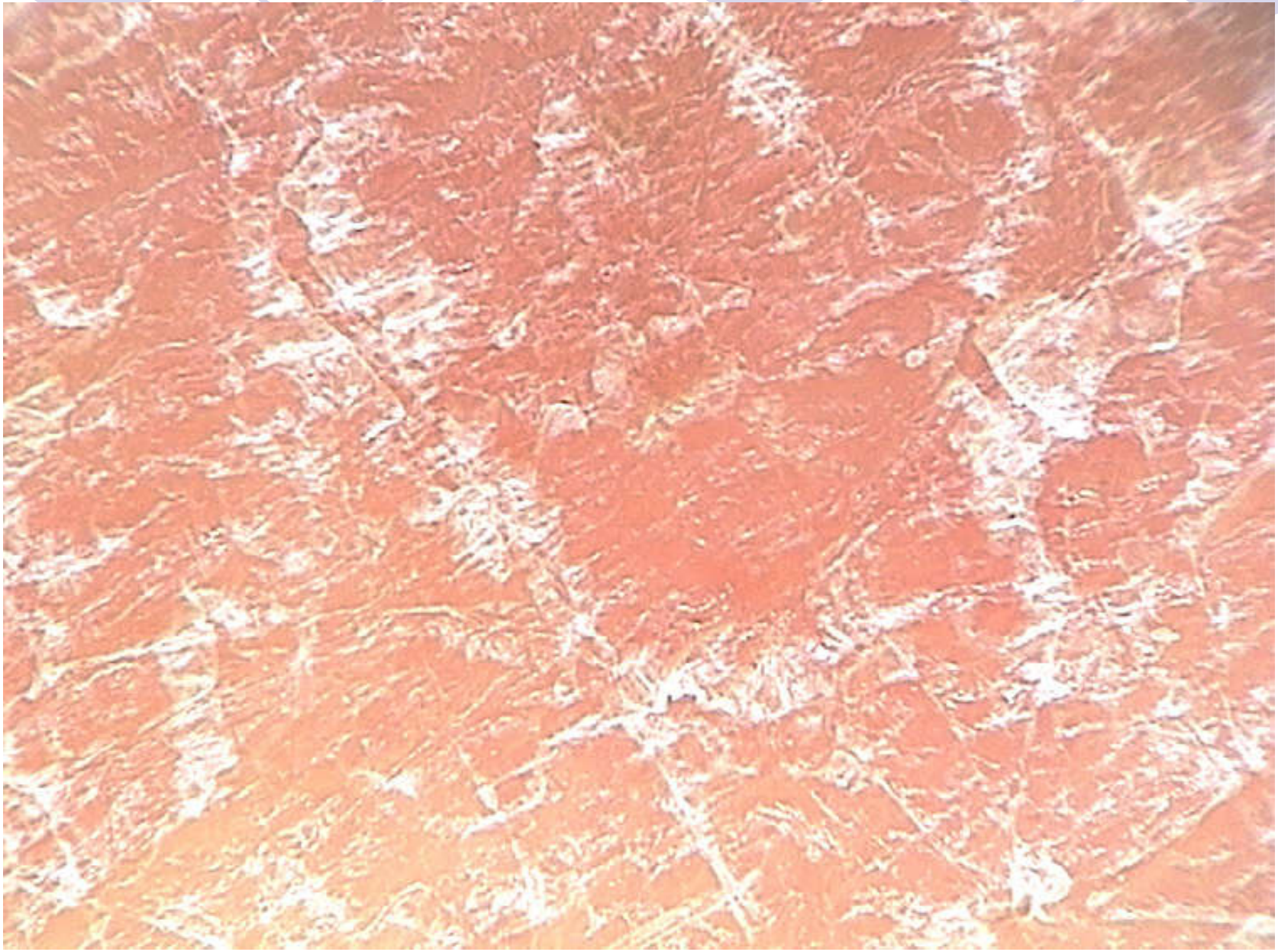
Case 1

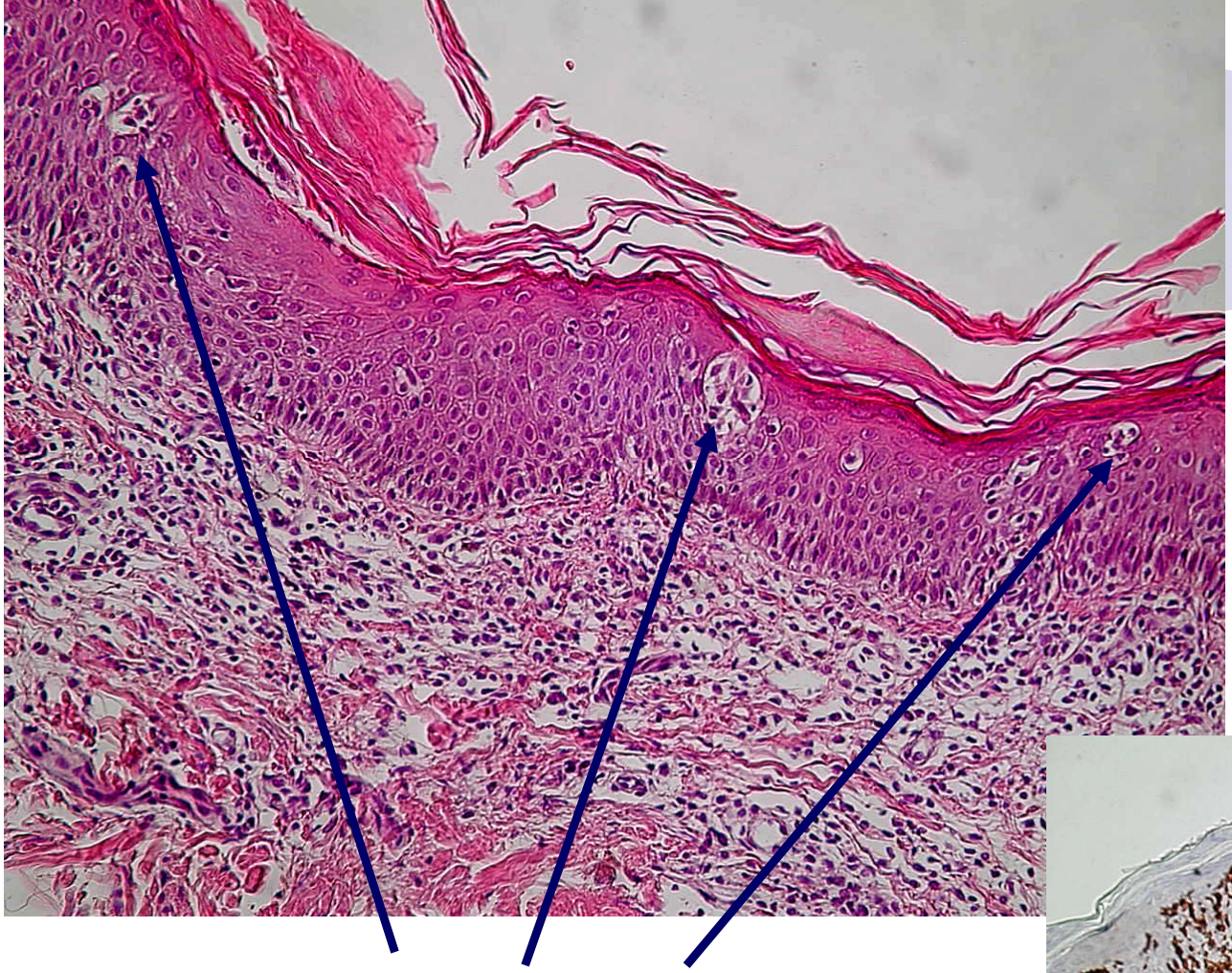
- 38-yo man with scaly erythematous patches present for three years
- itchy and worsening in fall and winter
- located in covered parts of the body
- persistent and expanding
- get better in a summer

Eczema? What kind?



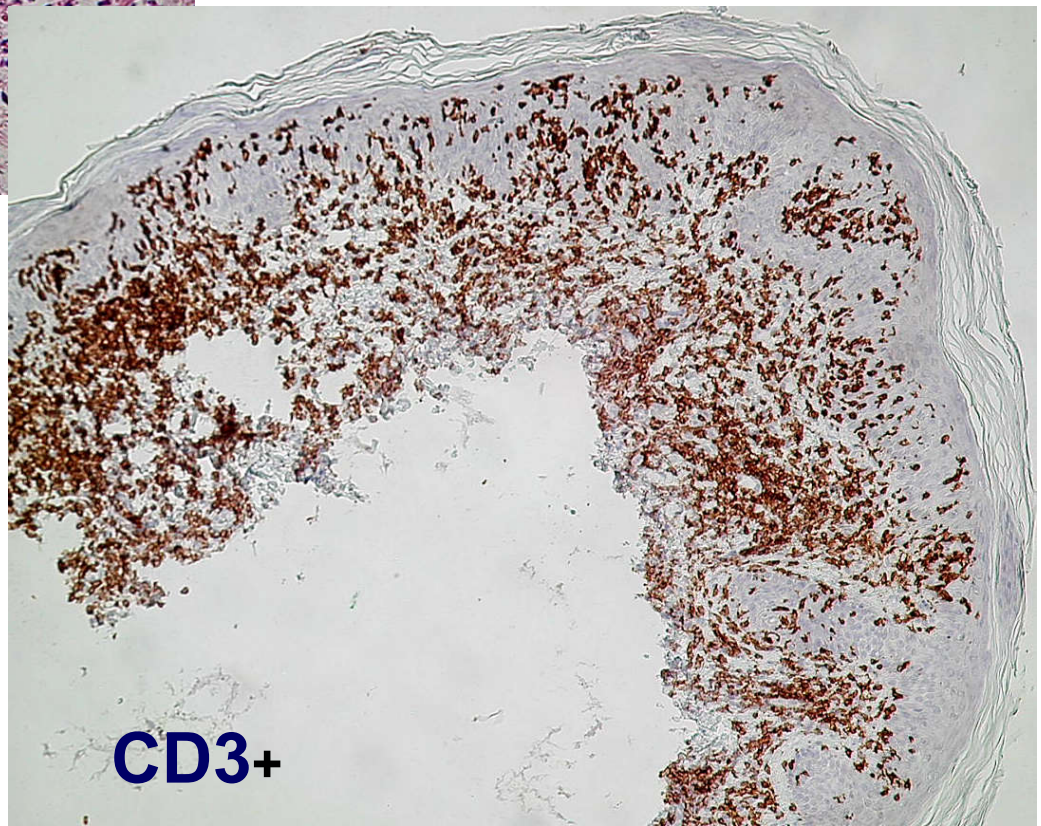
Dermoscopy examination – revealed pityriasiform scale

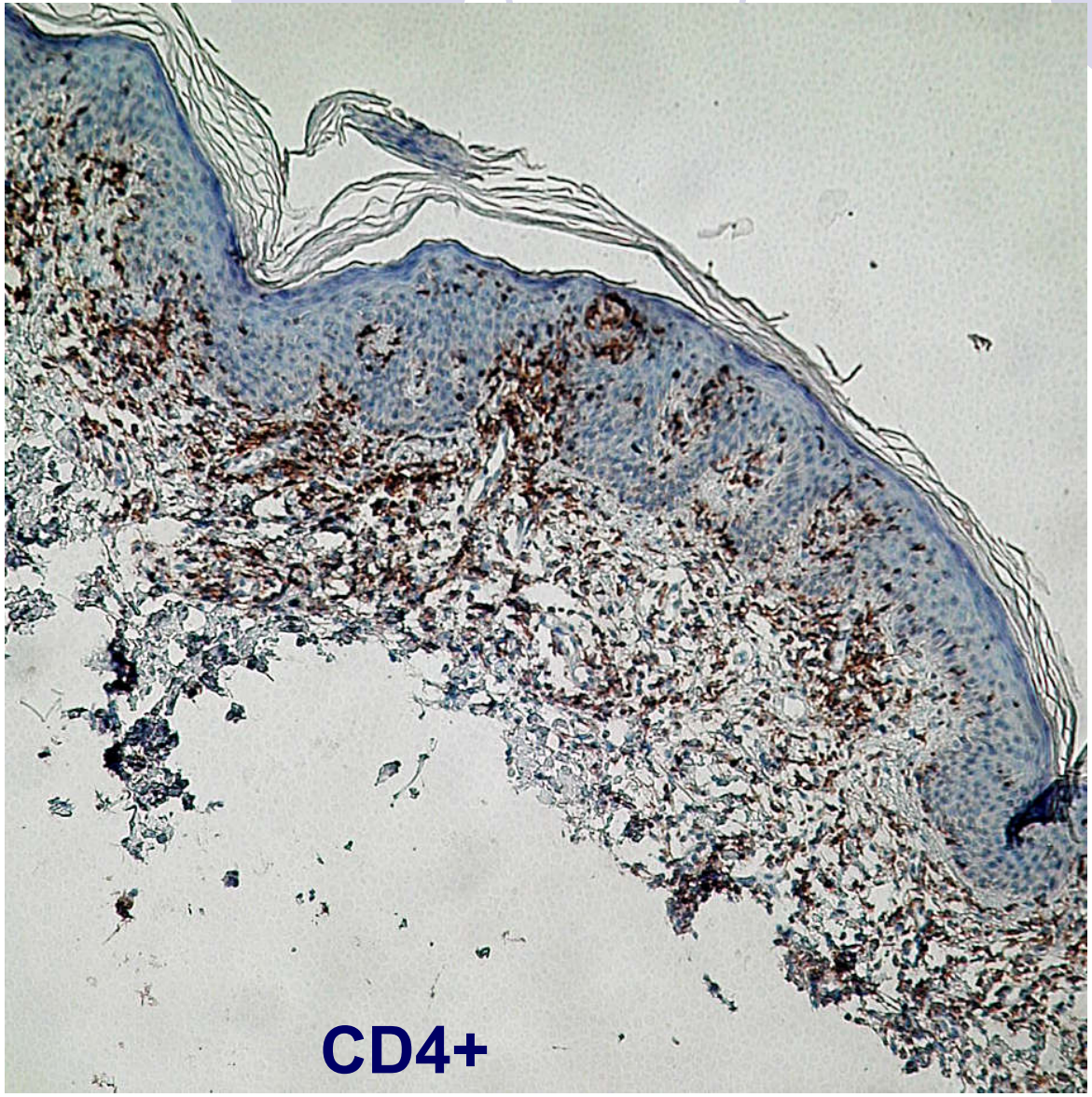


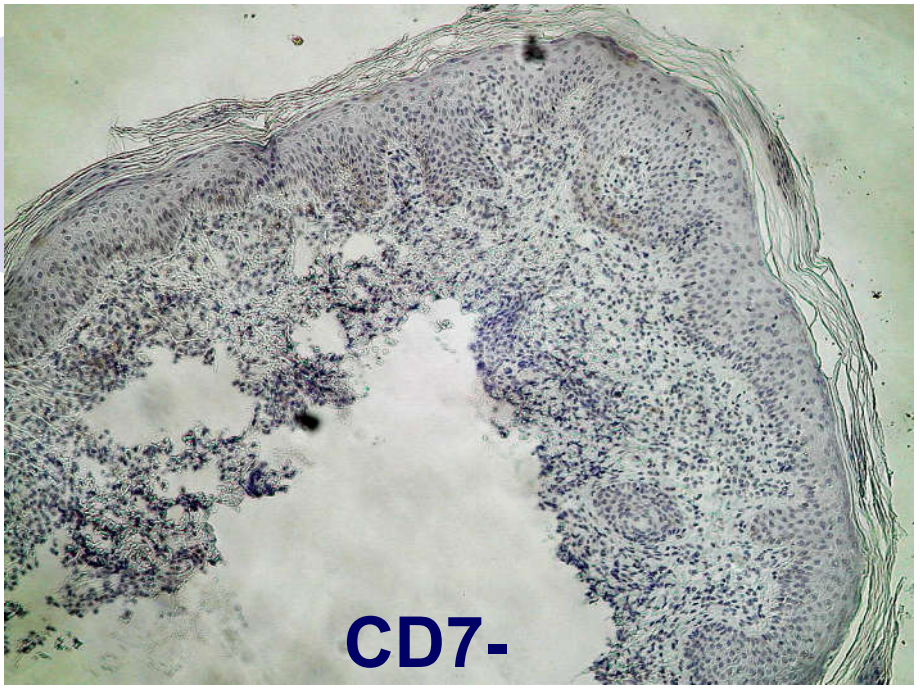


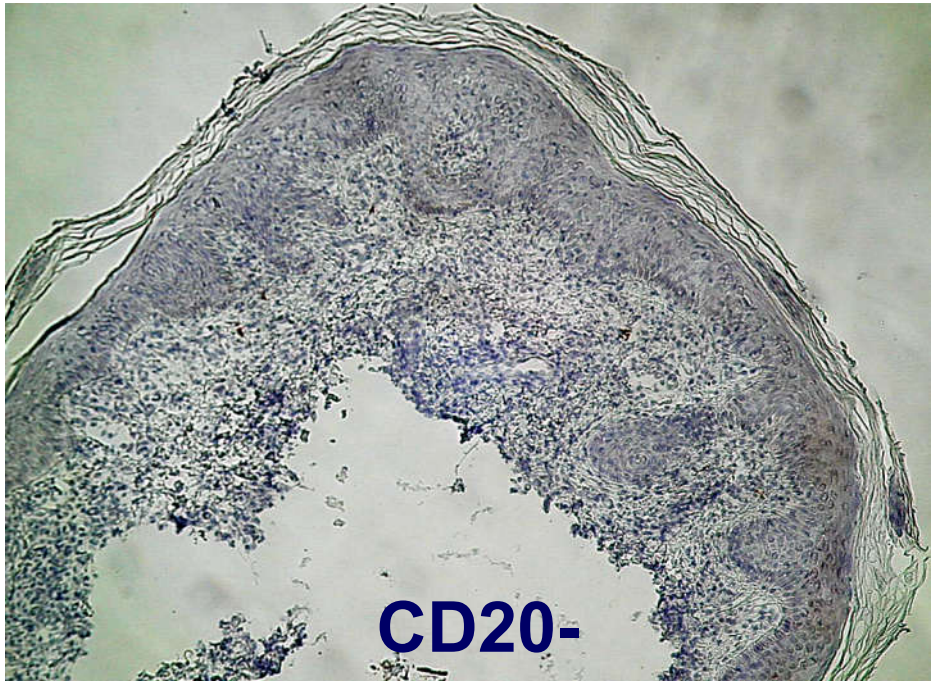
Epidermotropism

(presence of different cells than keratinocytes in the epidermis)




CD4+


CD7-


CD20-

Diagnosis ???

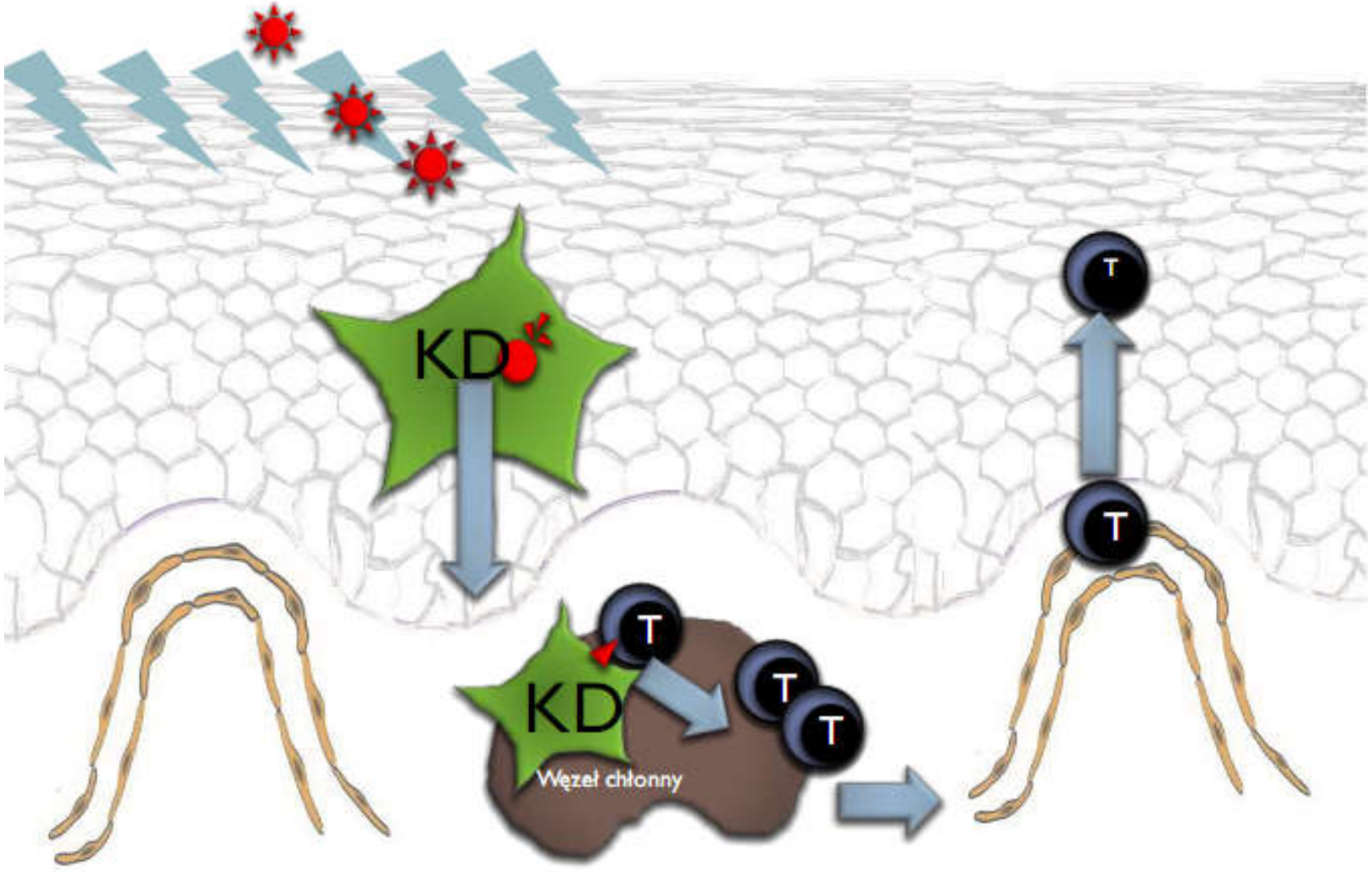
- Cutaneous T cell lymphoma (mycosis fungoides)
- patch stage – initial stage of mycosis fungoides
- scaly erythematous patches predominate
- mimics eczema but location on the trunk and on double covered parts of the body
- right diagnosis determinates treatment and prognosis

Mycosis fungoides

- T cell lymphoma which begins in the skin (primary cutaneous)
- remains localized in the skin for many years
- is a low-grade T cell lymphoma
- this is primarily CD4-positive helper T cell type
- it accounts for 50% of cutaneous lymphoma
- more common in blacks
- predilection for men (2:1)
- the age of incidence is over 40-yo
- occur more frequently in a population chronically exposed to chemical compounds, infections, occupational factors inducing genetic mutations

Chronic inflammation in the skin

Skin and lymph nodes



T cell lymphoma – clonal cell transformation and proliferation
One of theory – persitent hypersensitivity reaction

The risk factors link to MF development

- obesity (BMI > 30)
- long history of smoking
- work in the wood industry or agriculture are factors associated with an increased risk of mycosis fungoides development

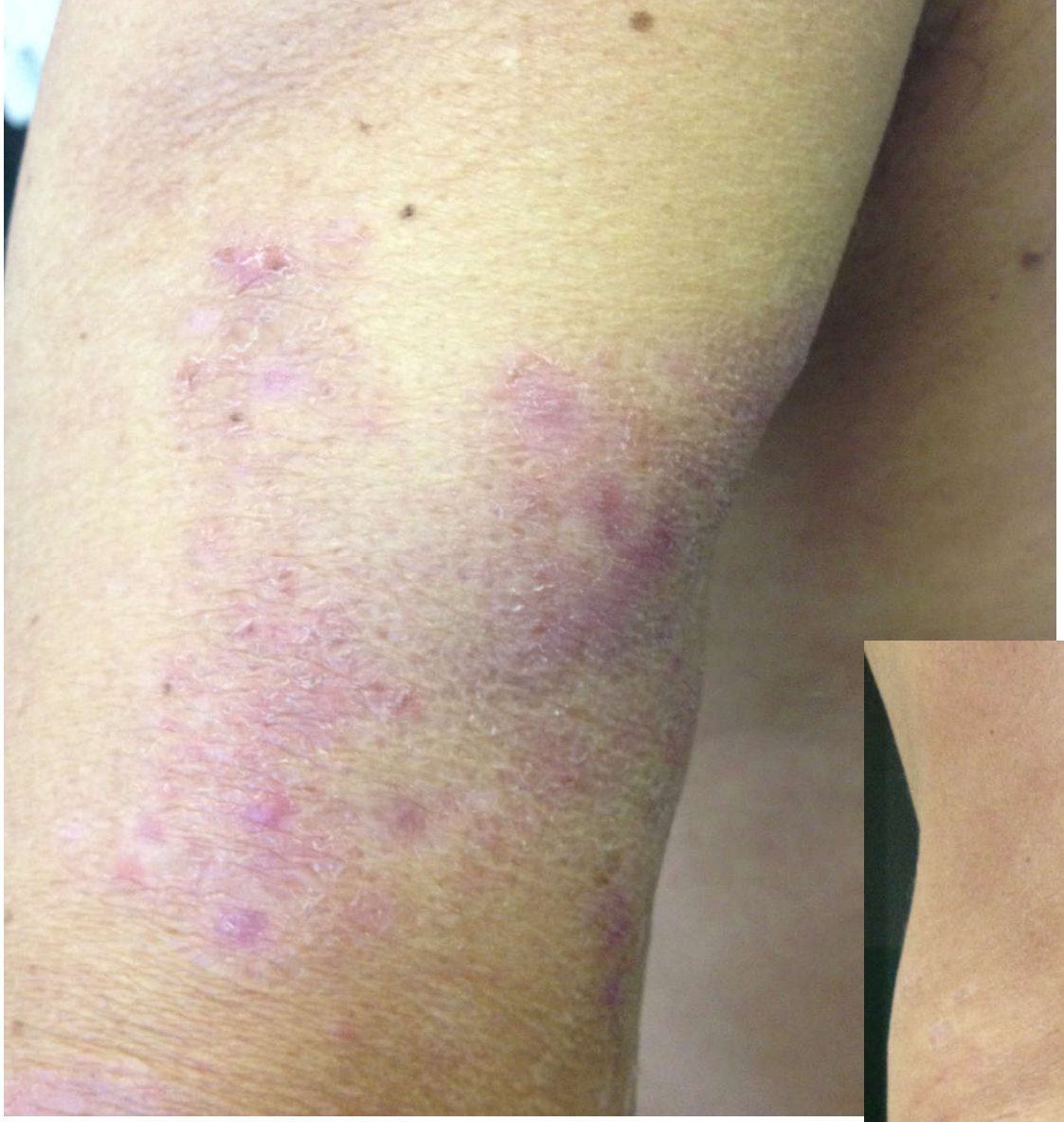
Clinical stages of mycosis fungoides

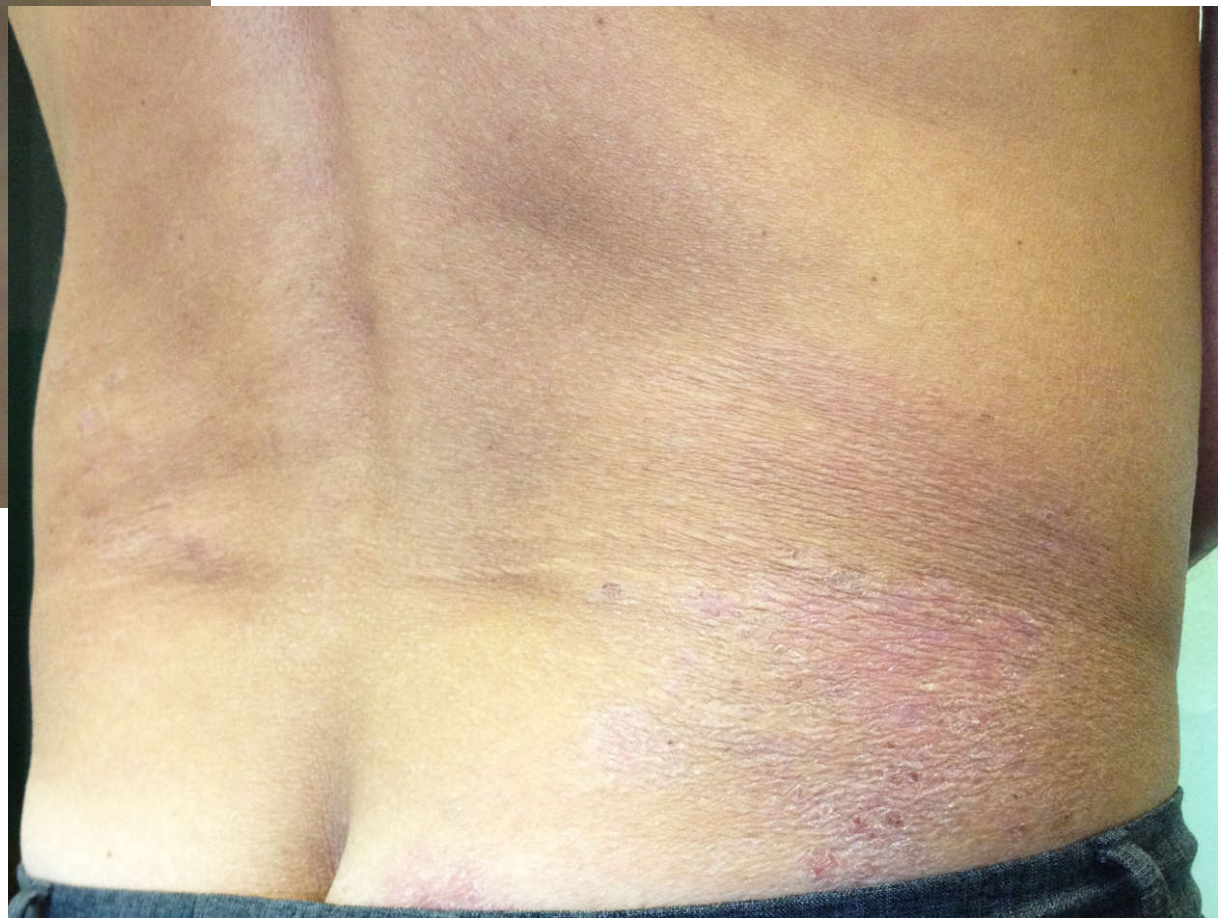
I phase	II phase	III phase
Time course 10-14 years	4-5 years	1-2 years
Patch stage Persistent scaly patches	Plaque stage Infiltrative elevated lesions	Tumor stage nodules

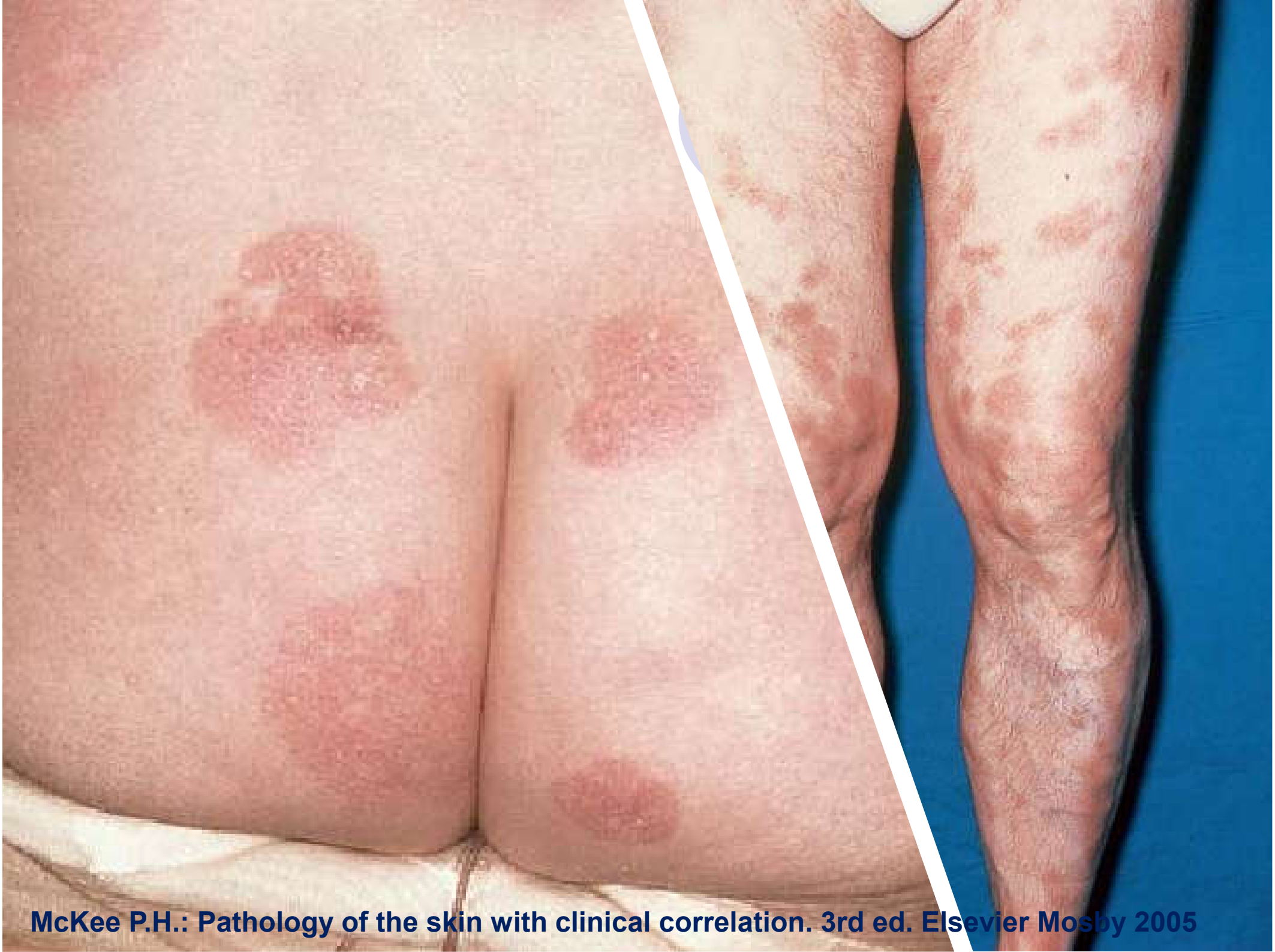
- Bazin 1876

MF – patch stage

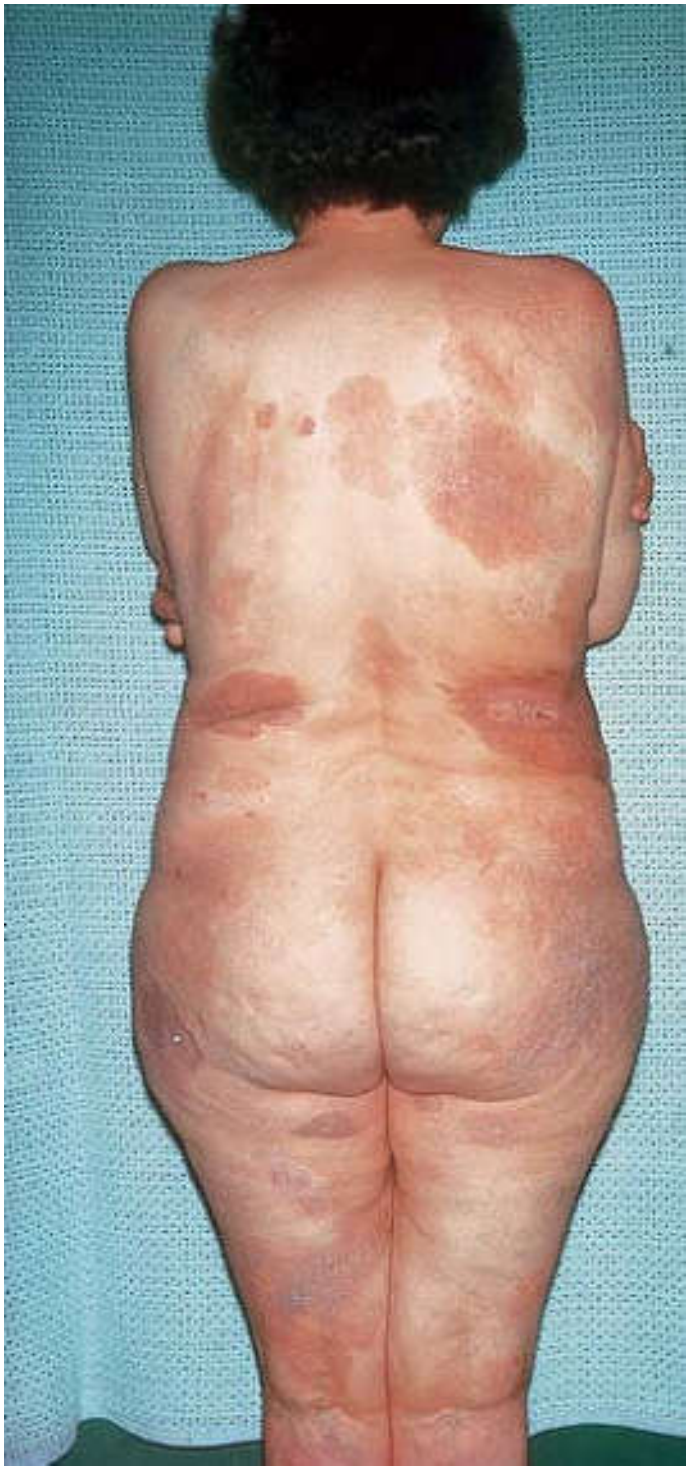
- the longest phase – 10 years of duration
- persistent scaly patches
- poor response to topical therapy with emollients and topical steroids
- pruritus -/+
- improvement after sun exposure
- in early stages, skin biopsy is frequently not diagnostic
- the average time from the onset of skin lesions to diagnosis is 4 years (7 years in the past)
- trunk and proximal extremities are affected (buttocks, breast, folds)
- irregularly shaped asymmetric, scaly, erythematous patches with telangiectasias

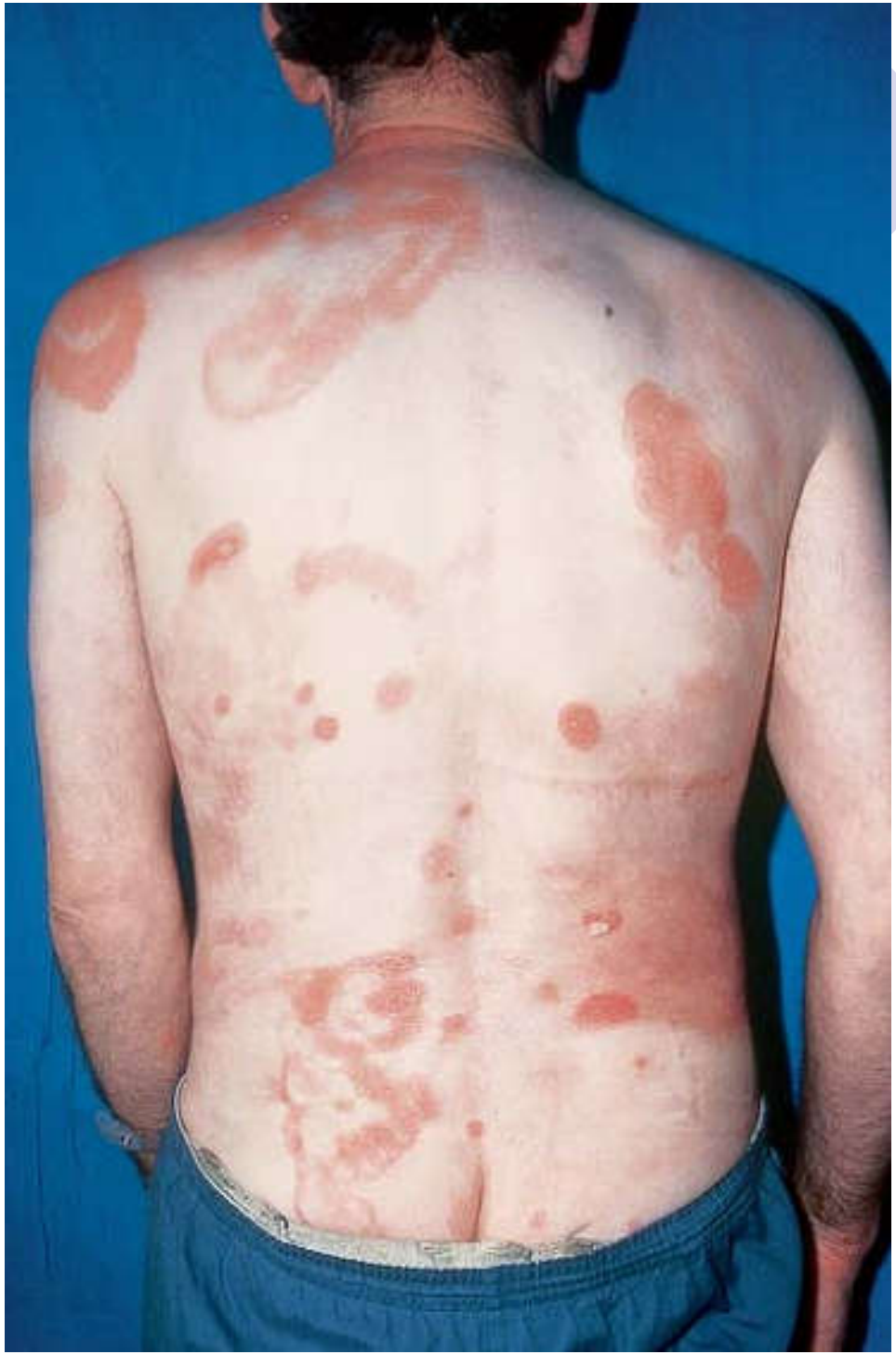






McKee P.H.: Pathology of the skin with clinical correlation. 3rd ed. Elsevier Mosby 2005

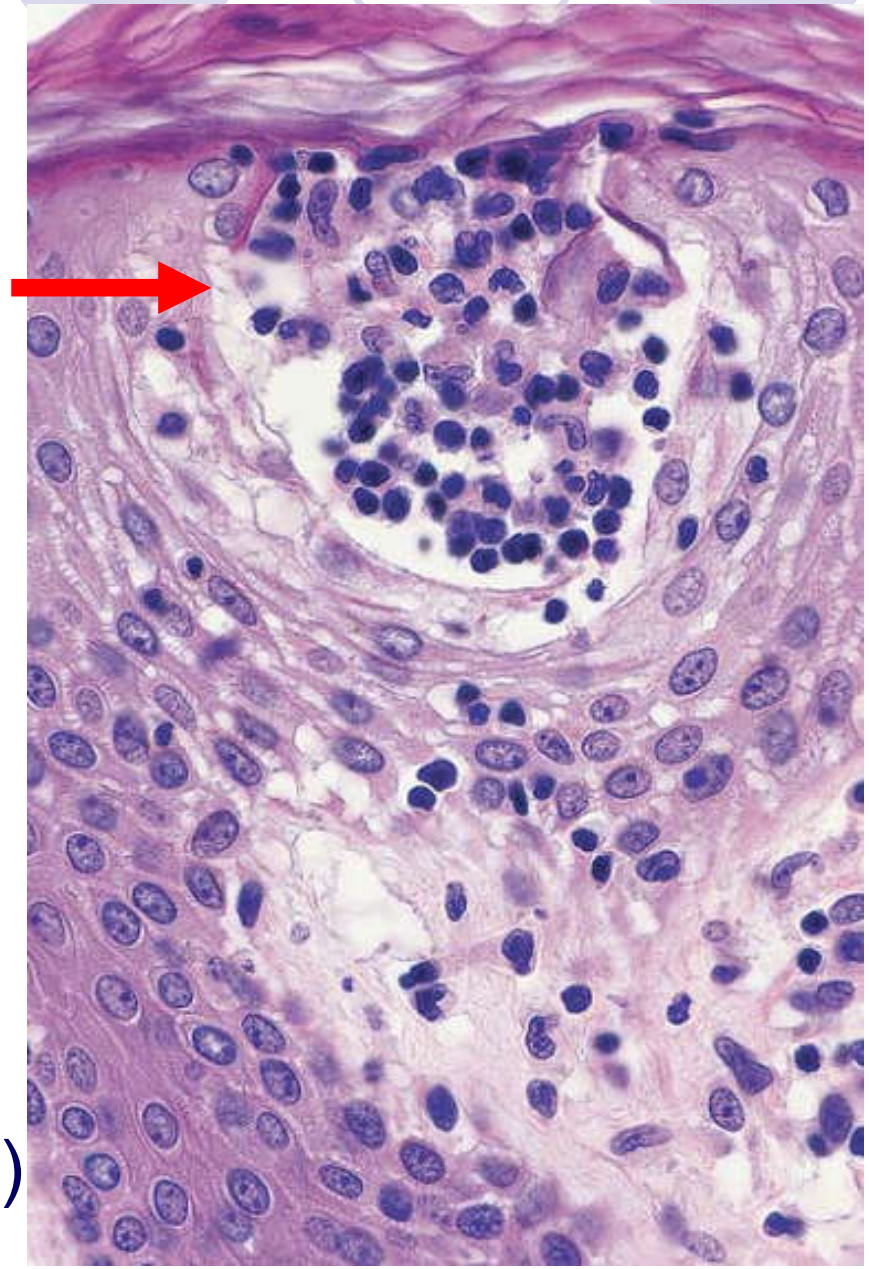




McKee P.H.: Pathology of the skin with clinical correlation. 3rd ed. Elsevier Mosby 2005

Histopathology of mycosis fungoides

- epidermotropism
- collections of lymphocytes in the epidermis (Pautrier microabscess) 25% „+”
- atypical lymphocytes 10%+
- subepidermal band-like lymphocytic infiltrate
- linear arrangement of single atypical lymphocytes at dermal-epidermal junction
- markers CD3+, CD4+, CD7-, CD5-
- monoclonal TCR
- cerebriform nuclear shape (ME)



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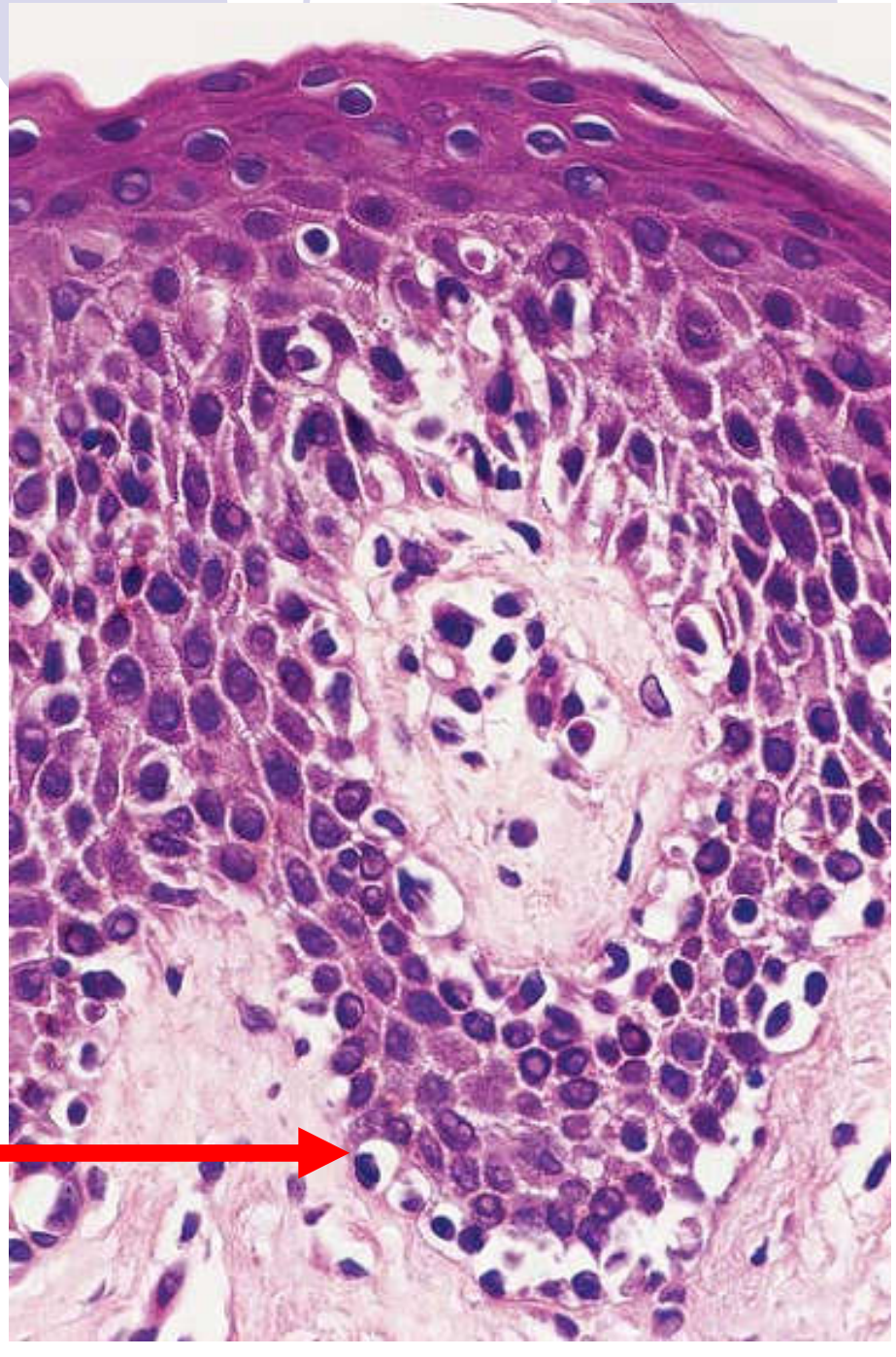
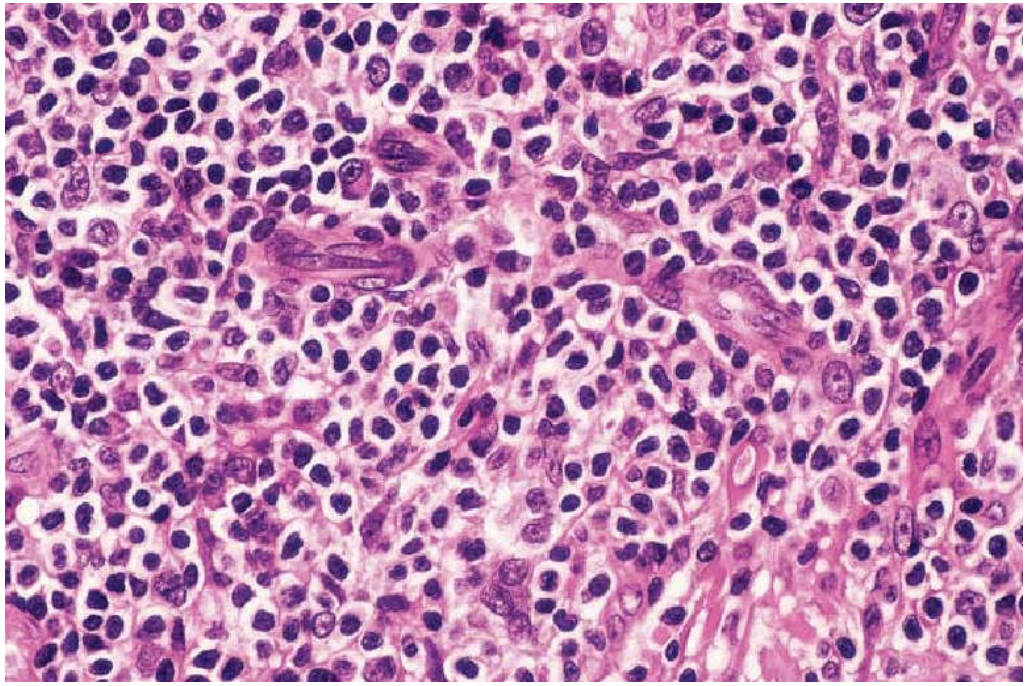
Mycosis fungoides

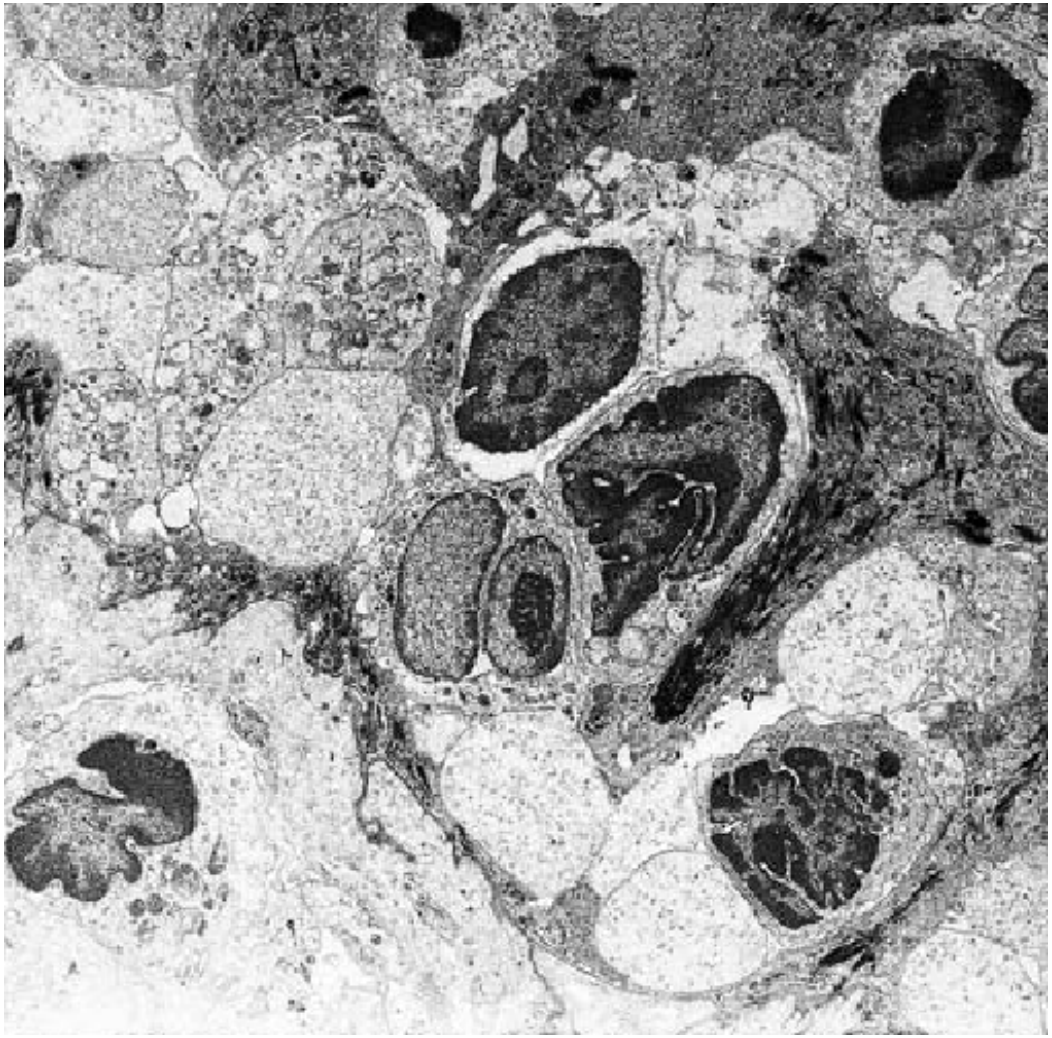
- Atypical lymphocytes „tagging” the DEJ



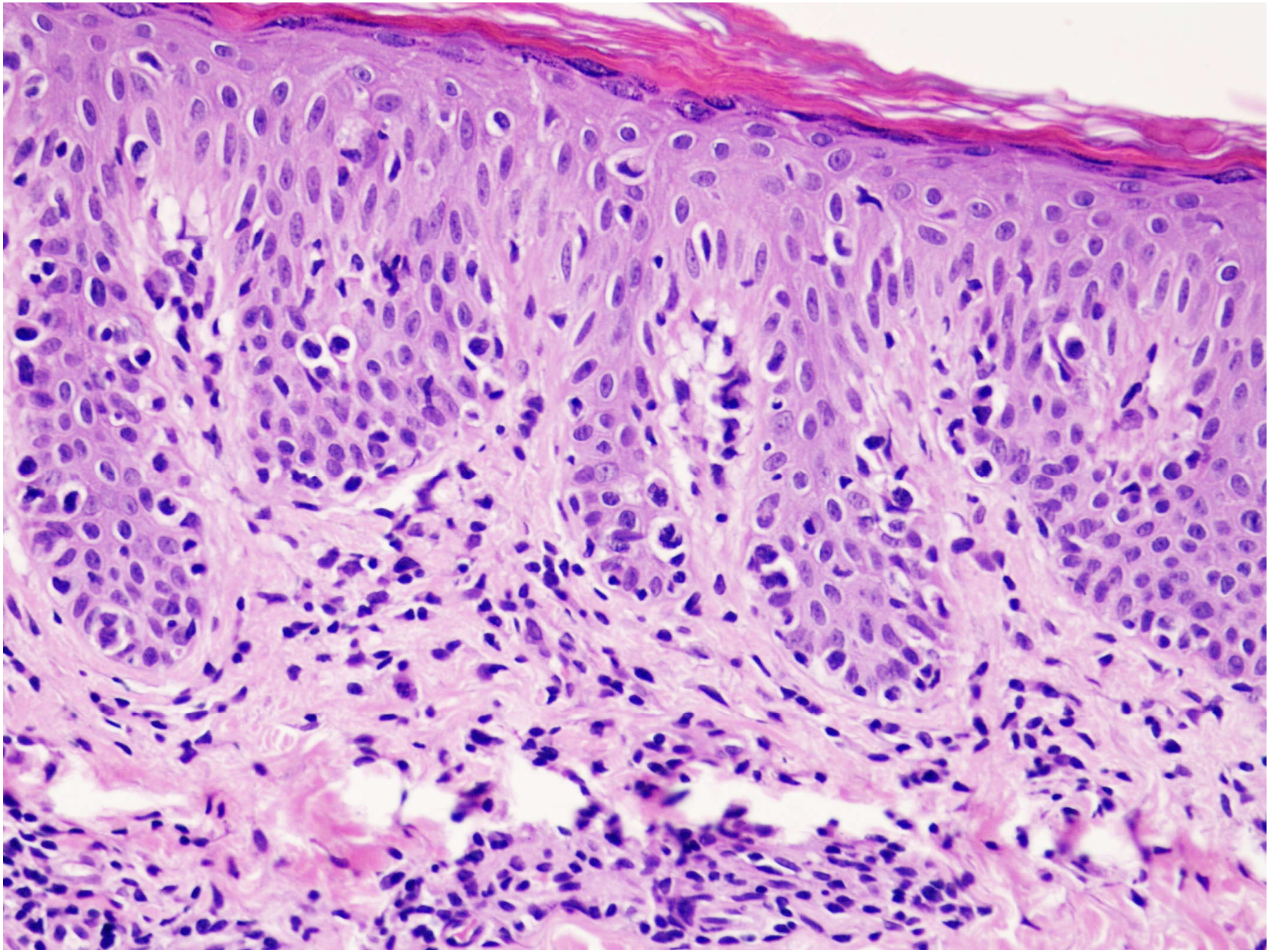
Atypical lymphocytes



Hyperchromatic and highly irregular nuclei with pericellular „halo”

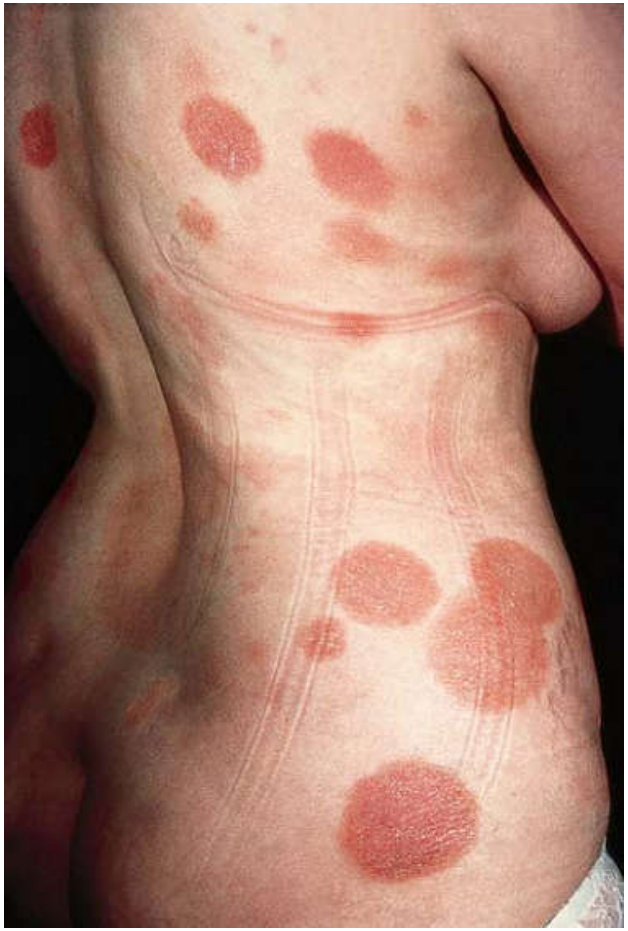


Highly convoluted (cerebriform) nuclei

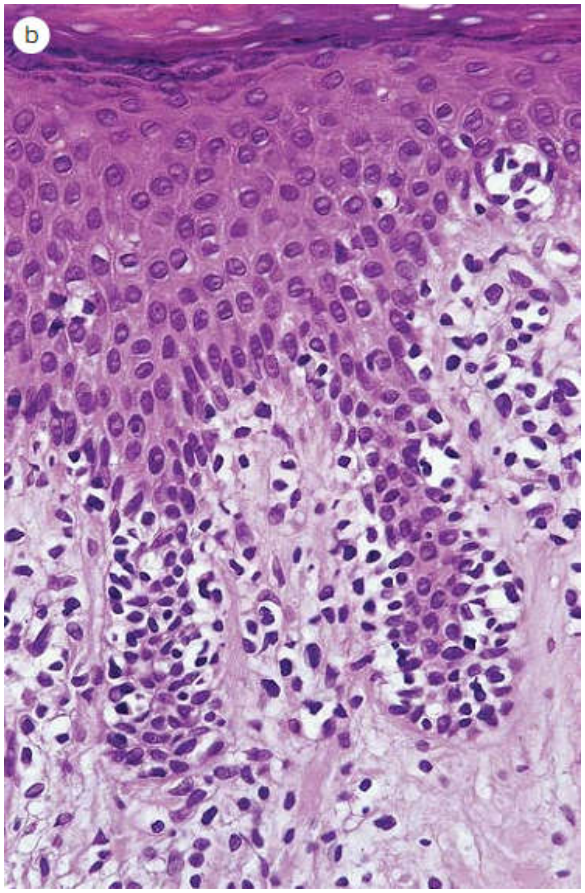


MF diagnosis

- Clinical lesions – suspected of MF



- Histopathology estimated in the context of clinical suspicion
- parapsoriasis/mycosis fungoides



MF diagnosis = clinical skin changes + histopathology

Clonality of T-cells

- MF (mycosis fungoides)
- PLEVA (*pityriasis lichenoides et varioliformis acuta*)
- lichen planus, lichen striatus
- lichen sclerosus
- atopic dermatitis
- lichenoid eczema, syphilis
- chronic actinic dermatitis
- pseudolymphoma (insect bite reaction, HSV infection, prolonged scabies, molluscum contagiosum, drug reactions)

Clinical-pathological correlation is needed to diagnose MF

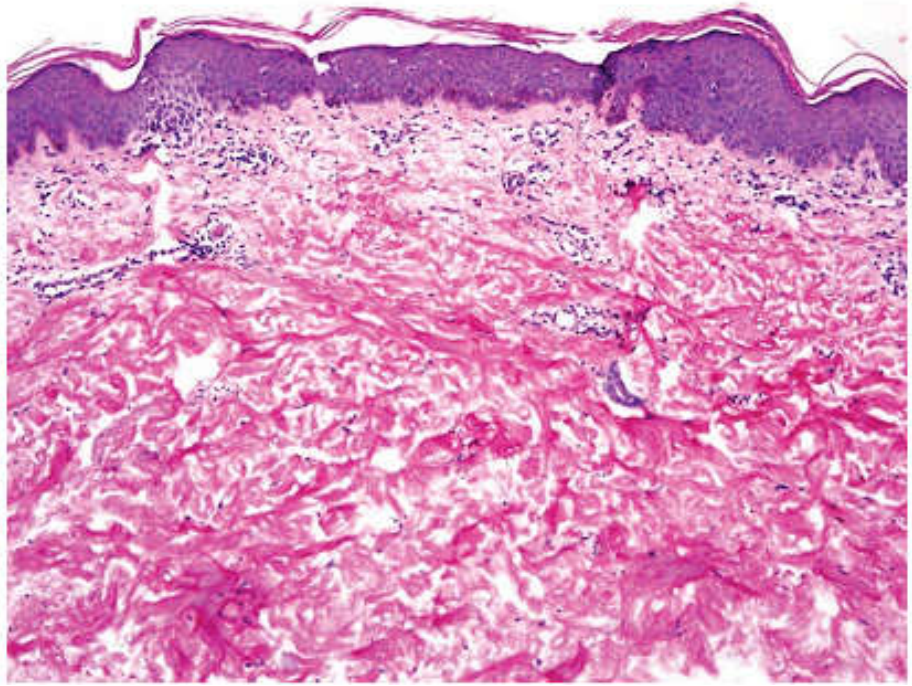
Mycosis Fungoides: An Updated Review of Clinicopathologic Variants

Christine S. Ahn, MD, Ahmed ALSayyah, MD,† and Omar P. Sangüeza, MD‡*

TABLE 1. Algorithm for the Diagnosis of Early MF. Adapted From Pimpinelli et al[6]

Criteria	Score
Clinical	
Basic	2 points for basic criteria and 2 additional criteria
Persistent and/or progressive patches/thin plaques	
Additional	2 points for basic criteria and 2 additional criteria
Non–sun-exposed location	
Size/shape variation	
Poikiloderma	
Histopathologic	
Basic	2 points for basic criteria and 2 additional criteria
Superficial lymphoid infiltrate	
Additional	
Epidermotropism without spongiosis	1 point for basic criteria and 1 additional criterion
Lymphoid atypia defined as cells with enlarged hyperchromatic nuclei and irregular or cerebriform nuclear contours	
Molecular biological	
Clonal TCR gene rearrangement	1 point for clonality
Immunopathologic	
Less than 50% $CD2^+$, $CD3^+$, and/or $CD5^+$ T cells	1 point for one or more criteria
Less than 10% $CD7^+$ T cells	
Epidermal/dermal discordance of CD2, CD3, CD5, or CD7	

TCR, T-cell receptor.



Early Mycosis Fungoides

- perform several biopsies if early mycosis fungoides is suspected to establish the proper diagnosis.

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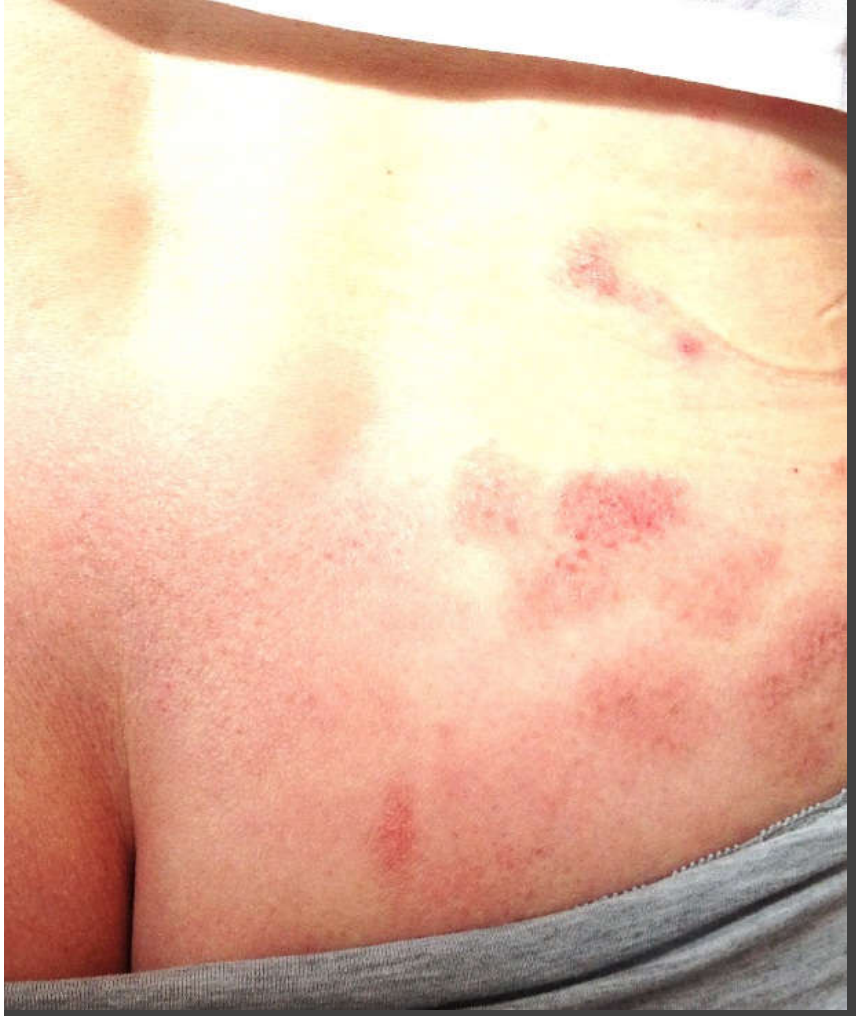
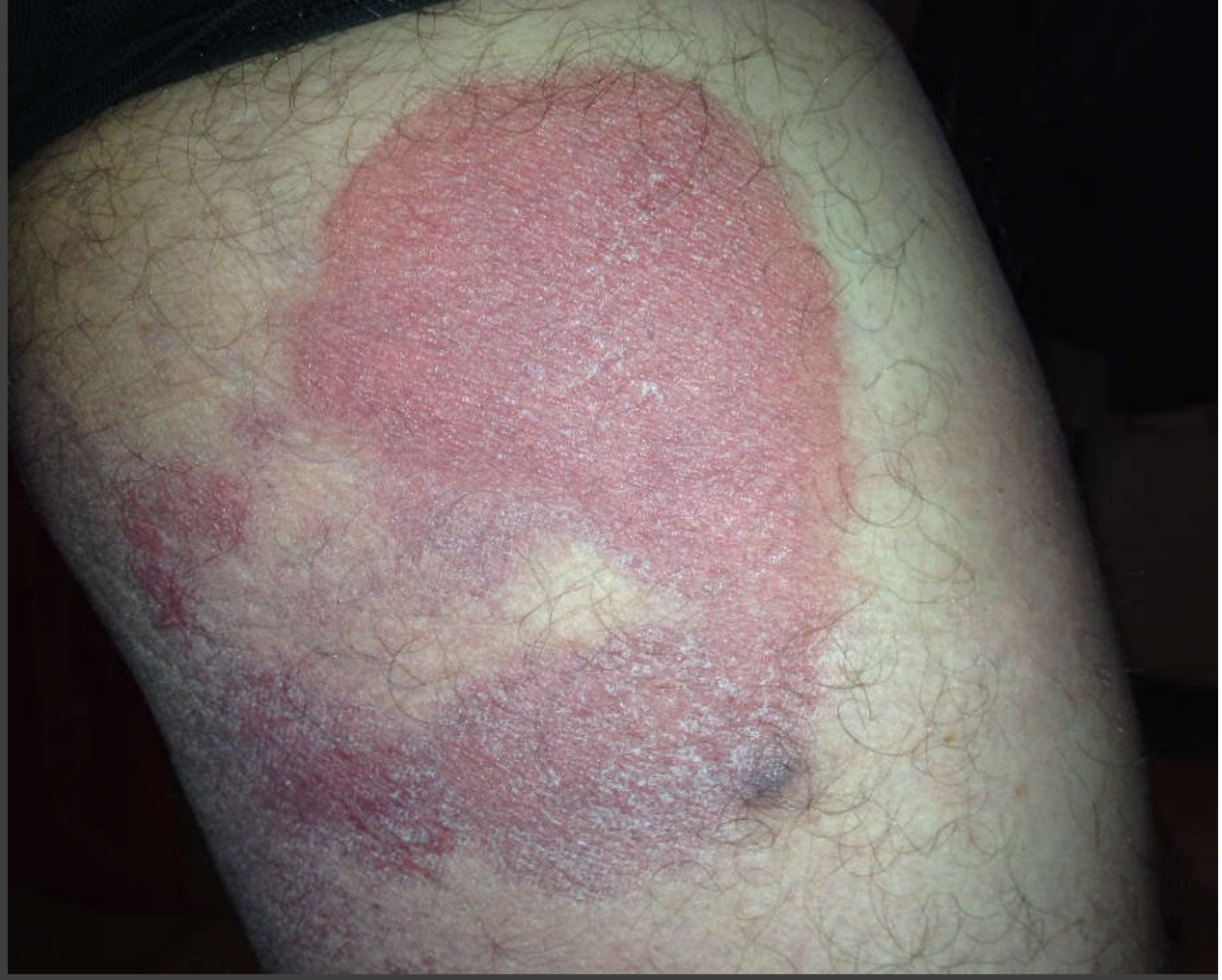
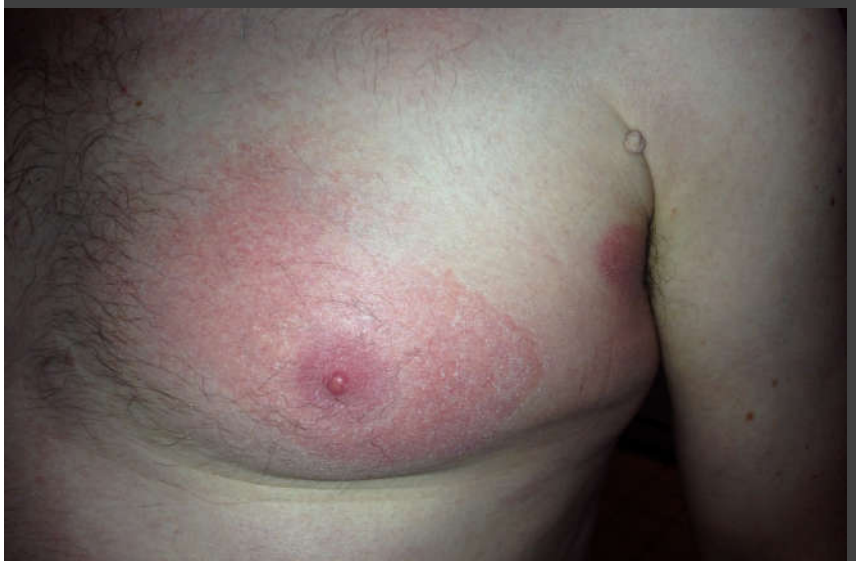
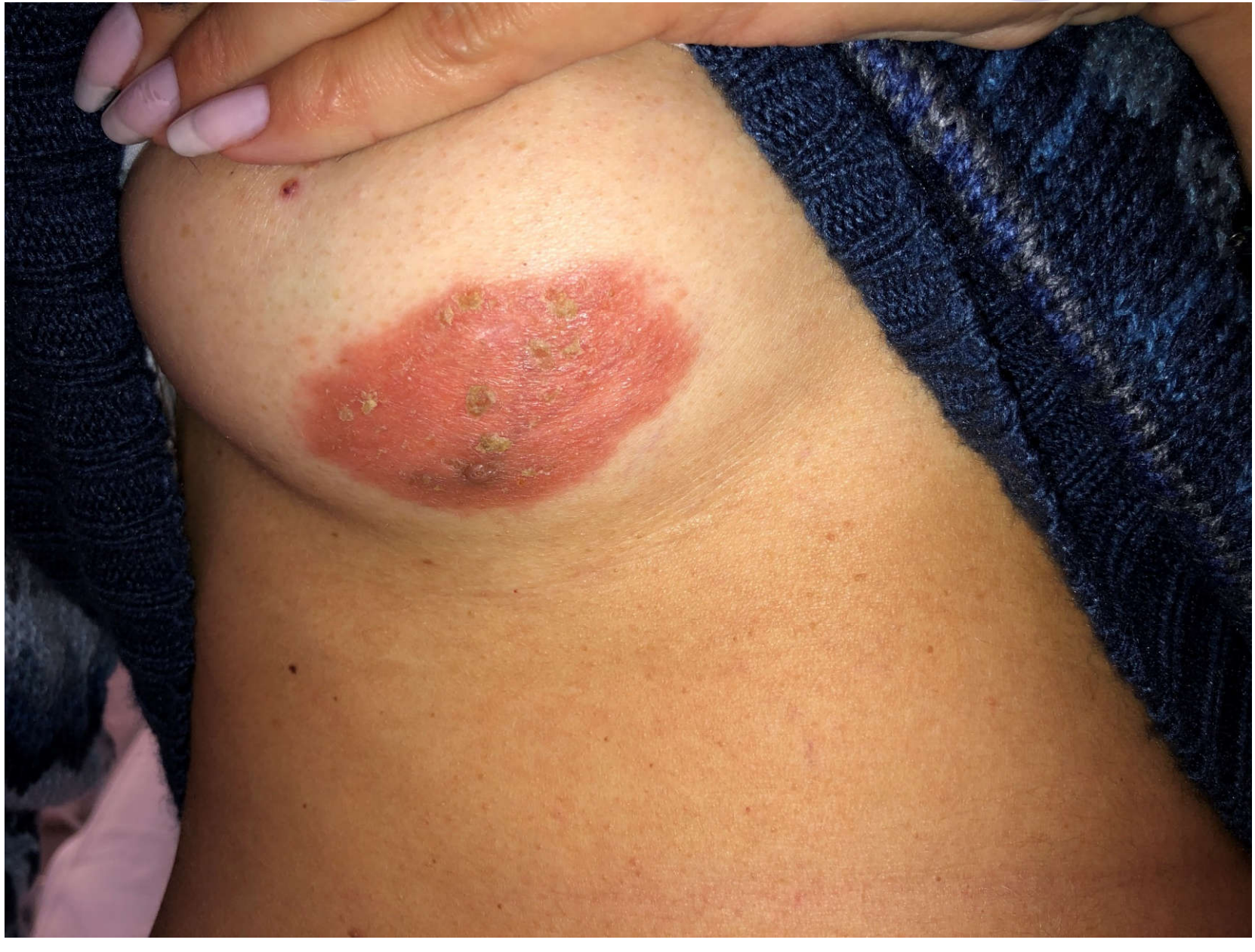




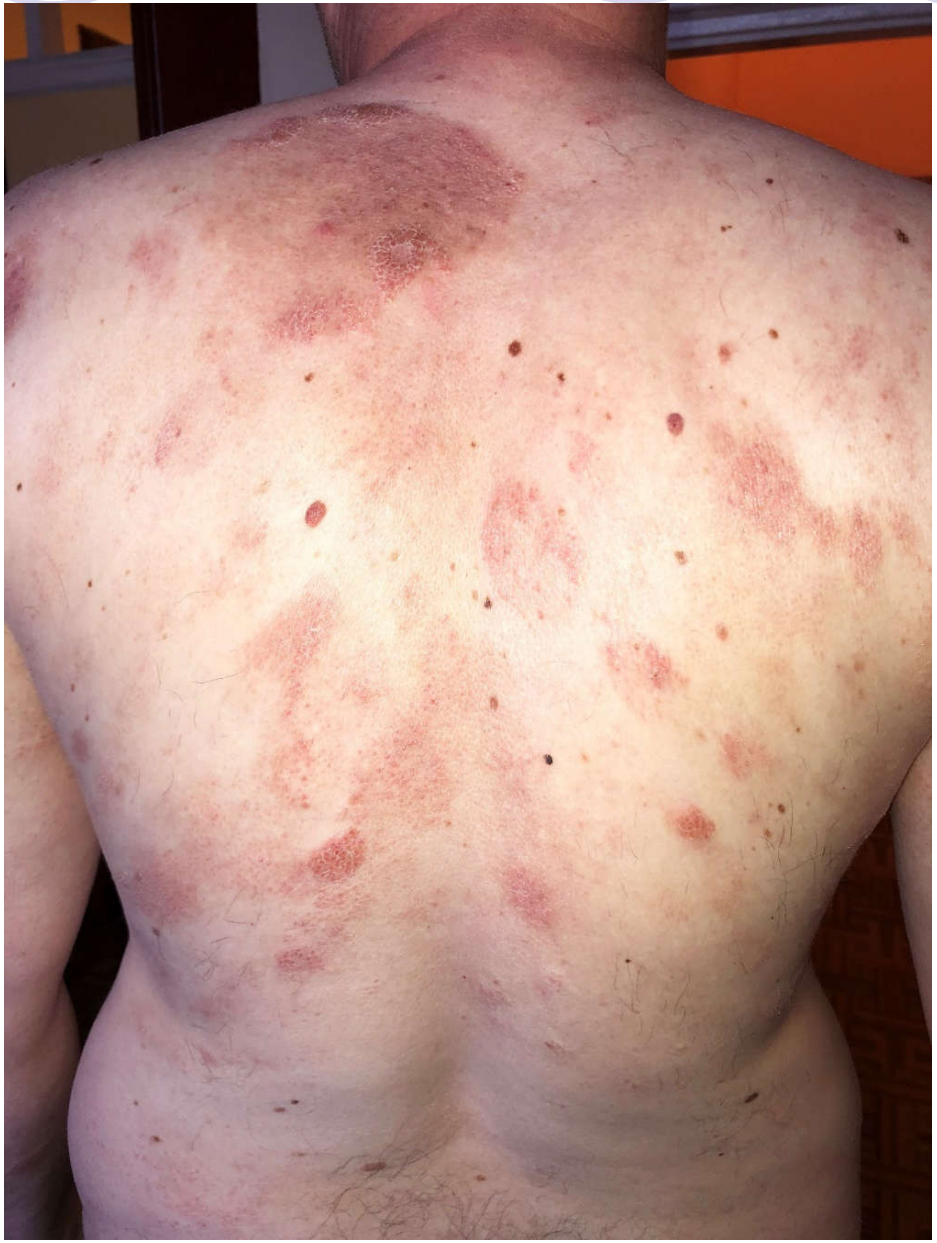


Oval, round or kidney-shaped erythematous scaly skin lesions in sun protected or double covered locations

Mycosis fungoides – only one location, duration over 3 years, persistent



Mycosis fungoides in a patient with contact dermatitis – difficult for histopathological evaluation due to overlapping eczema with MF



Clinical stages of MF and Sezary Syndrome in TNMB

TNMB CLASSIFICATION OF MYCOSIS FUNGOIDES AND SÉZARY SYNDROME	
T (SKIN)	
T_1	Limited patch/plaque (involving <10% of total skin surface)
T_2	Generalized patch/plaque (involving ≥10% of total skin surface)
T_3	Tumor(s)
T_4	Erythroderma
N (LYMPH NODE)	
N_0	No enlarged lymph nodes
N_1	Enlarged lymph nodes, histologically uninvolved
N_2	Enlarged lymph nodes, histologically involved (nodal architecture uneffaced)
N_3	Enlarged lymph nodes, histologically involved (nodal architecture [partially] effaced)
M (VISCERA)	
M_0	No visceral involvement
M_1	Visceral involvement
B (BLOOD)	
B_0	No circulating atypical (Sézary) cells (or <5% of lymphocytes)
B_1	Low blood tumor burden (≥5% of lymphocytes are Sézary cells, but not B_2)
B_2	High blood tumor burden (≥1000/µl Sézary cells + positive clone)

lungs
GI tract
liver
spleen

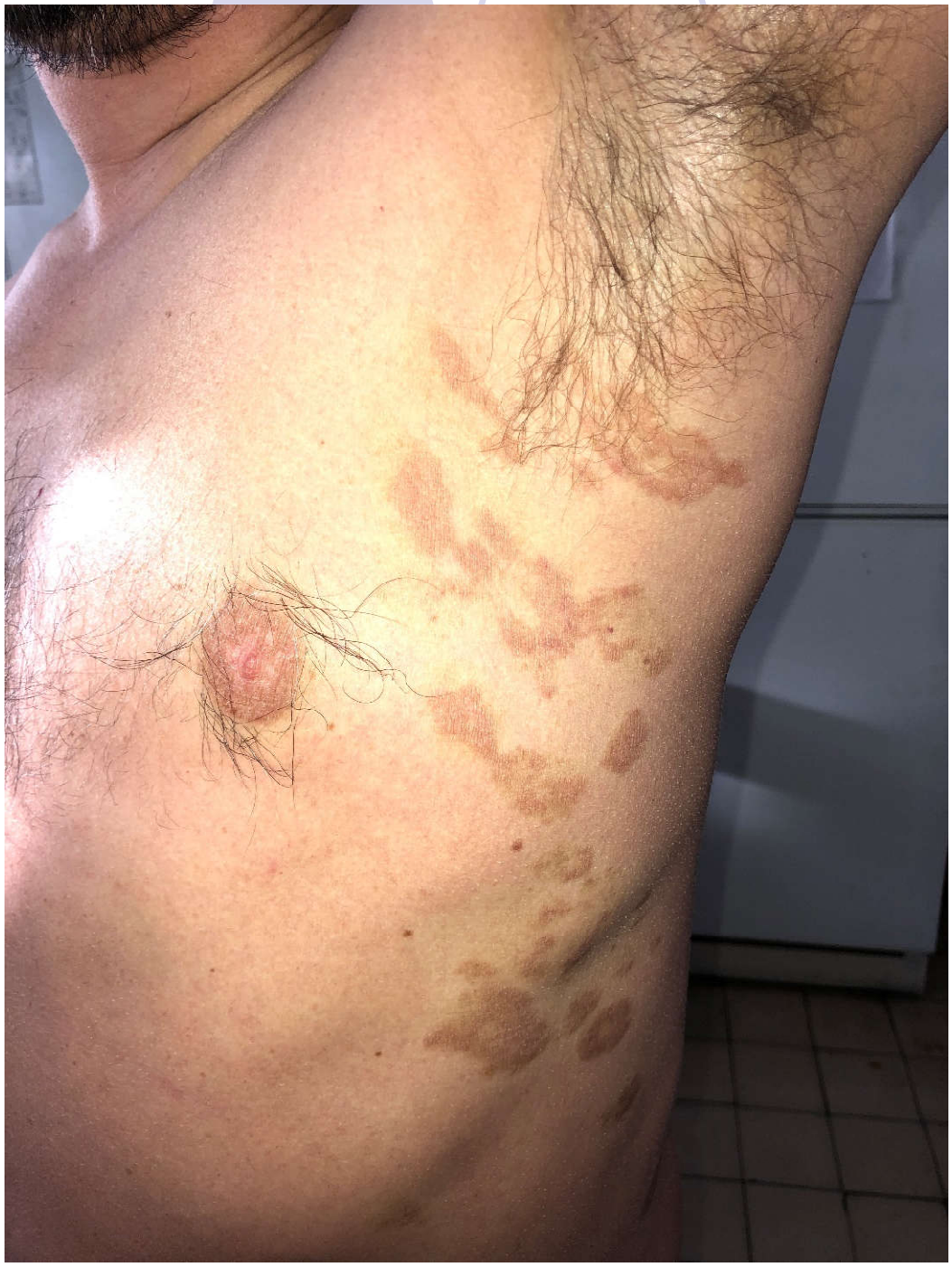
MF treatment – dermatological for years

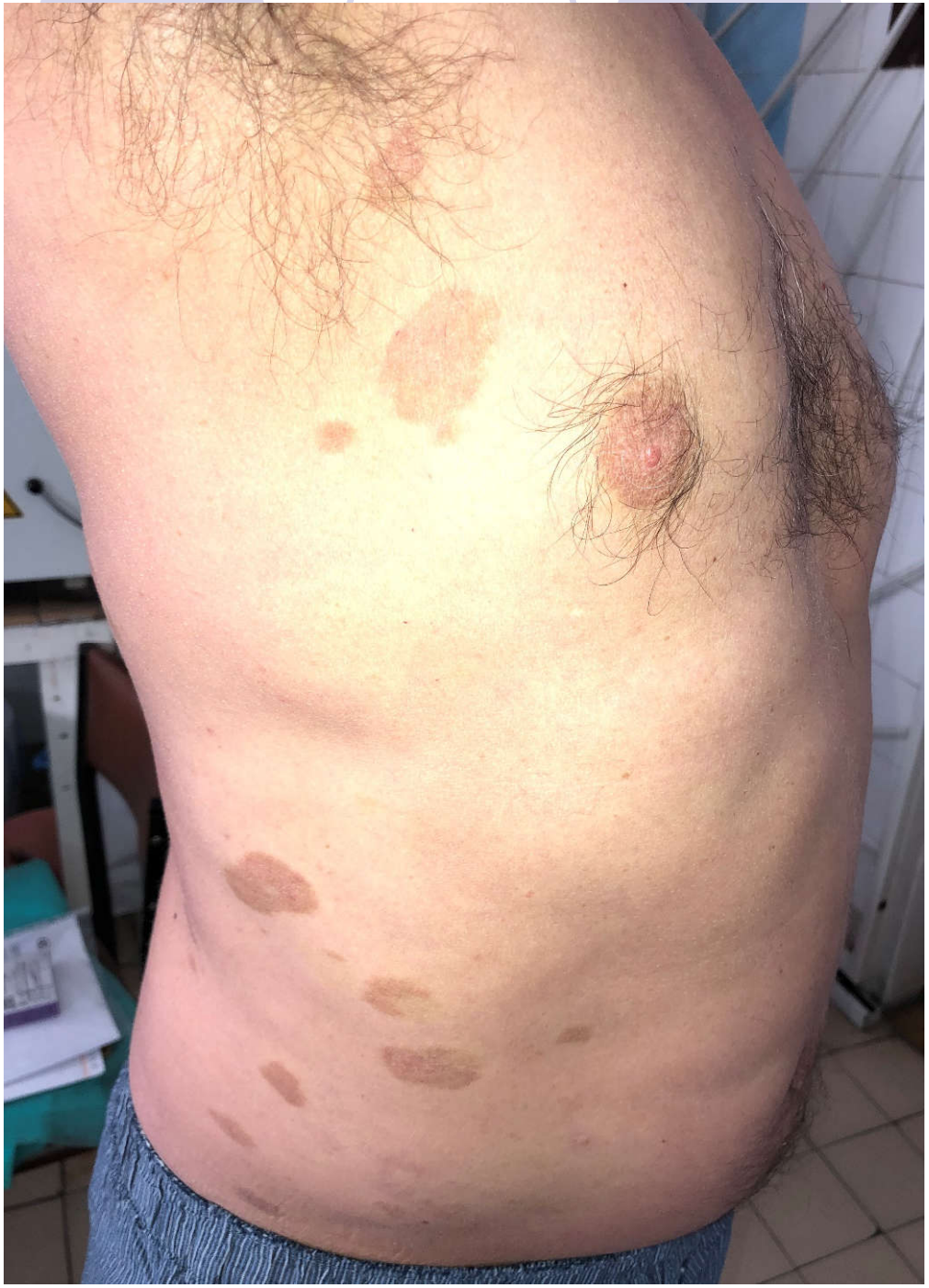
Accordingly to the stage of MF

- Topical: moderate to potent corticosteroids, carmustine
- Phototherapy: PUVA, Re-PUVA, NB-UVB (311nm)
- Oral retinoids (bexaroten, acitretin)
- extracorporeal photophoresis (the FDA-approved)
- electron-beam therapy
- INF-alfa
- chemotherapy
- radiotherapy

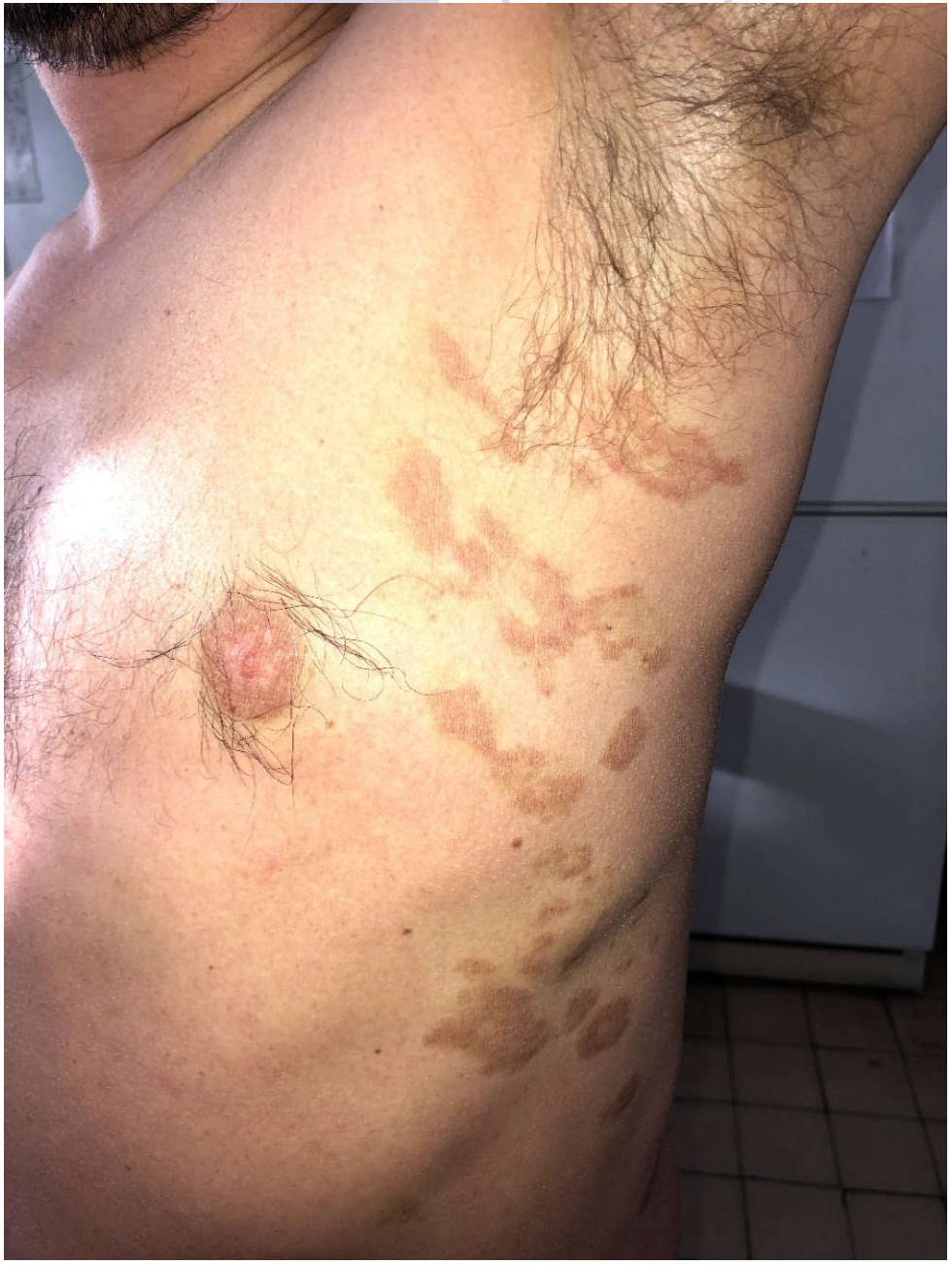
Complete remissions are common, especially in the early-stage of the disease!

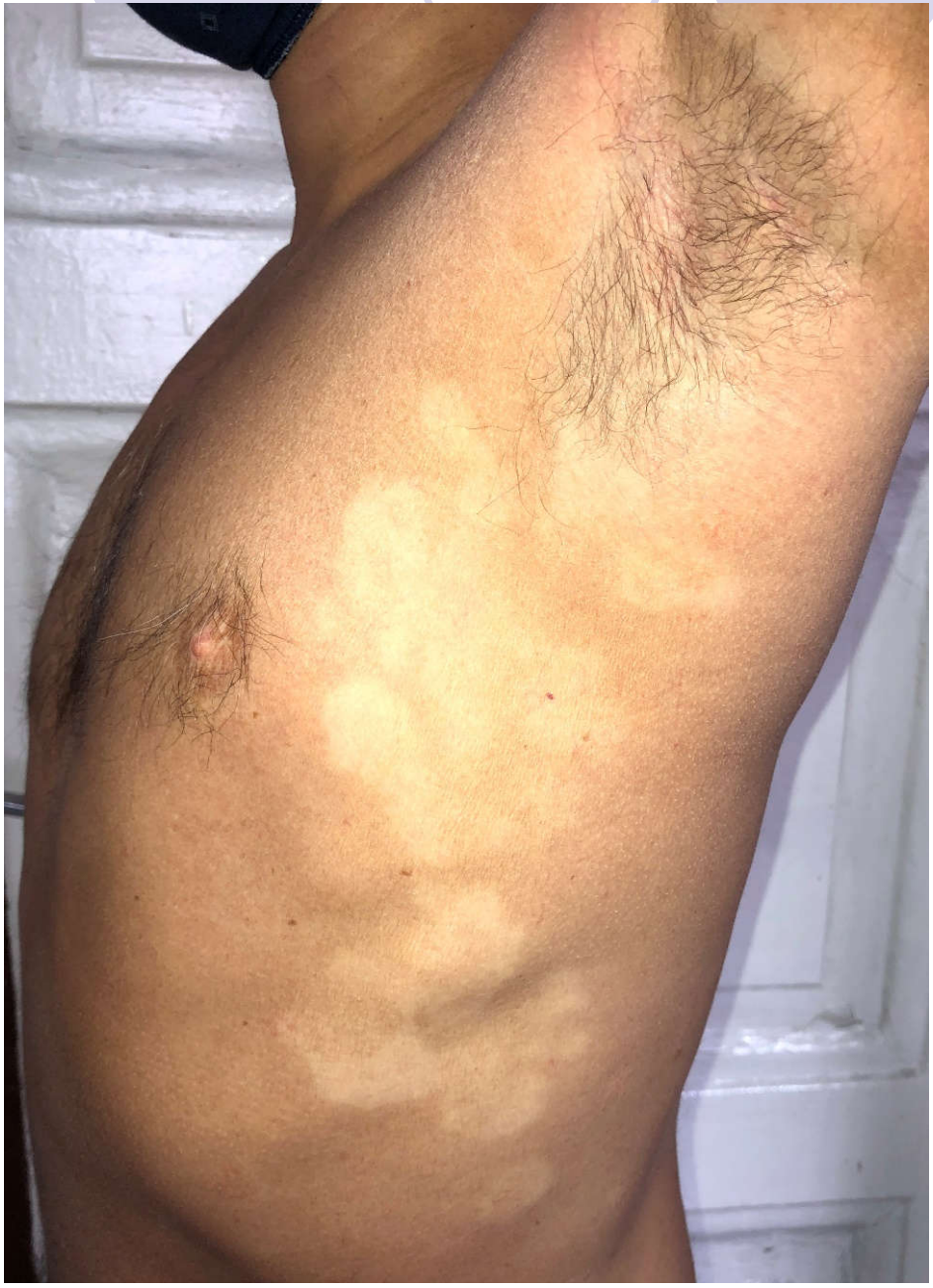
Mycosis fungoides on Re-PUVA therapy





Remission of mycosis fungoides after Re-PUVA – postinflammatory hypopigmentation



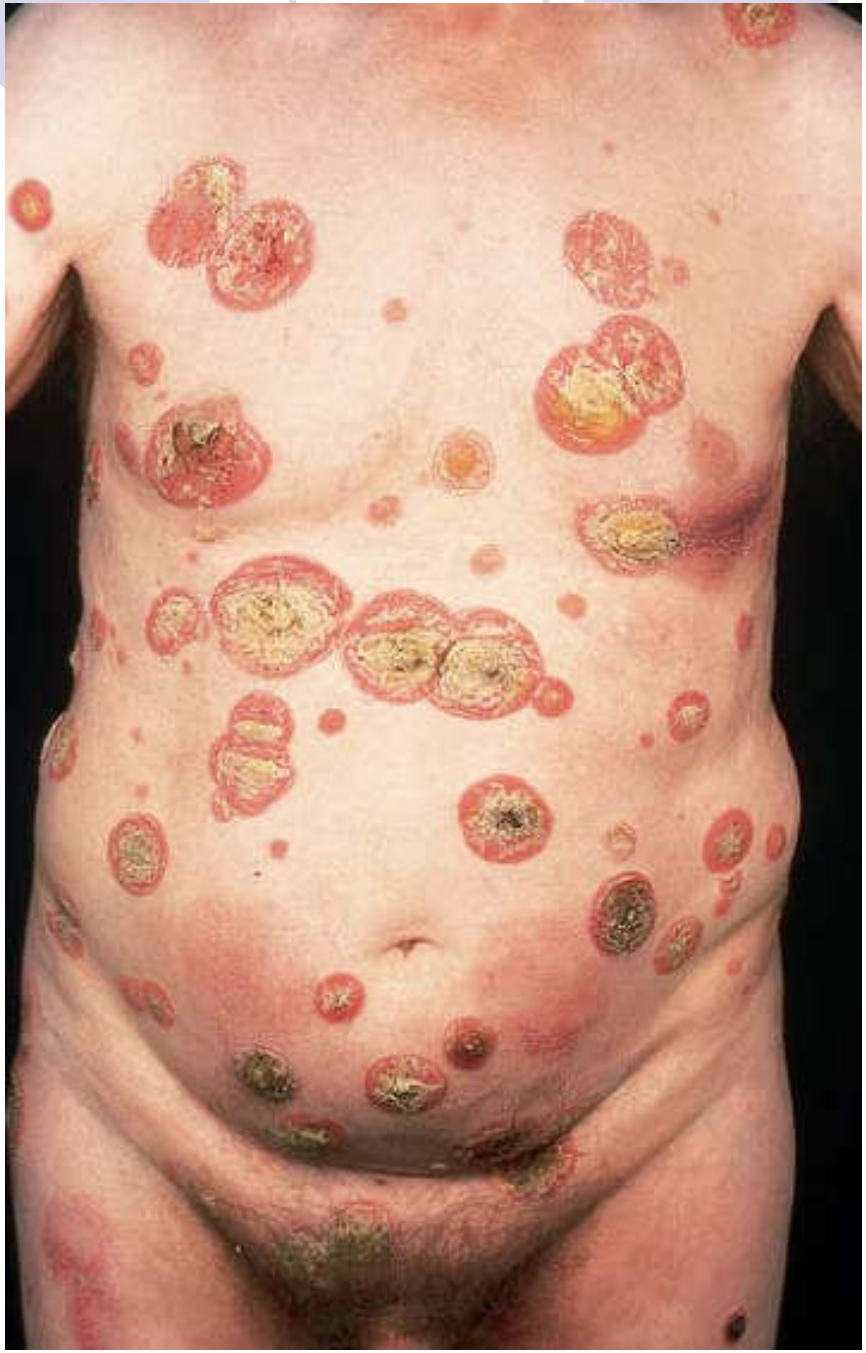


Bexaroten (Targretin)

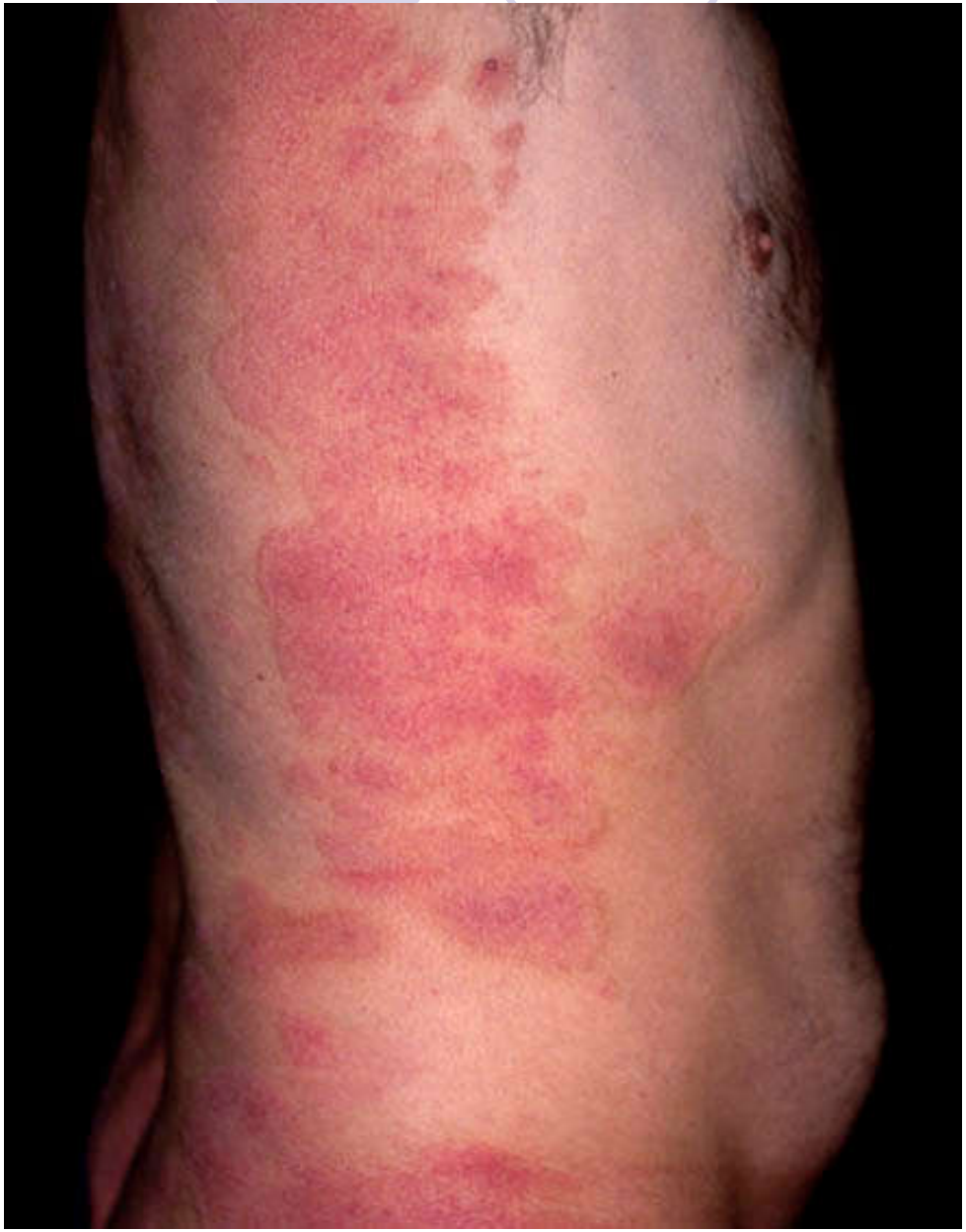
- synthetic retinoid
- selectively activates retinoid X receptors - rexinoid
- oral form at recommended dose is 300 mg/m^2
- teratogenic drug
- topical form as the gel is also available (Targretin gel)

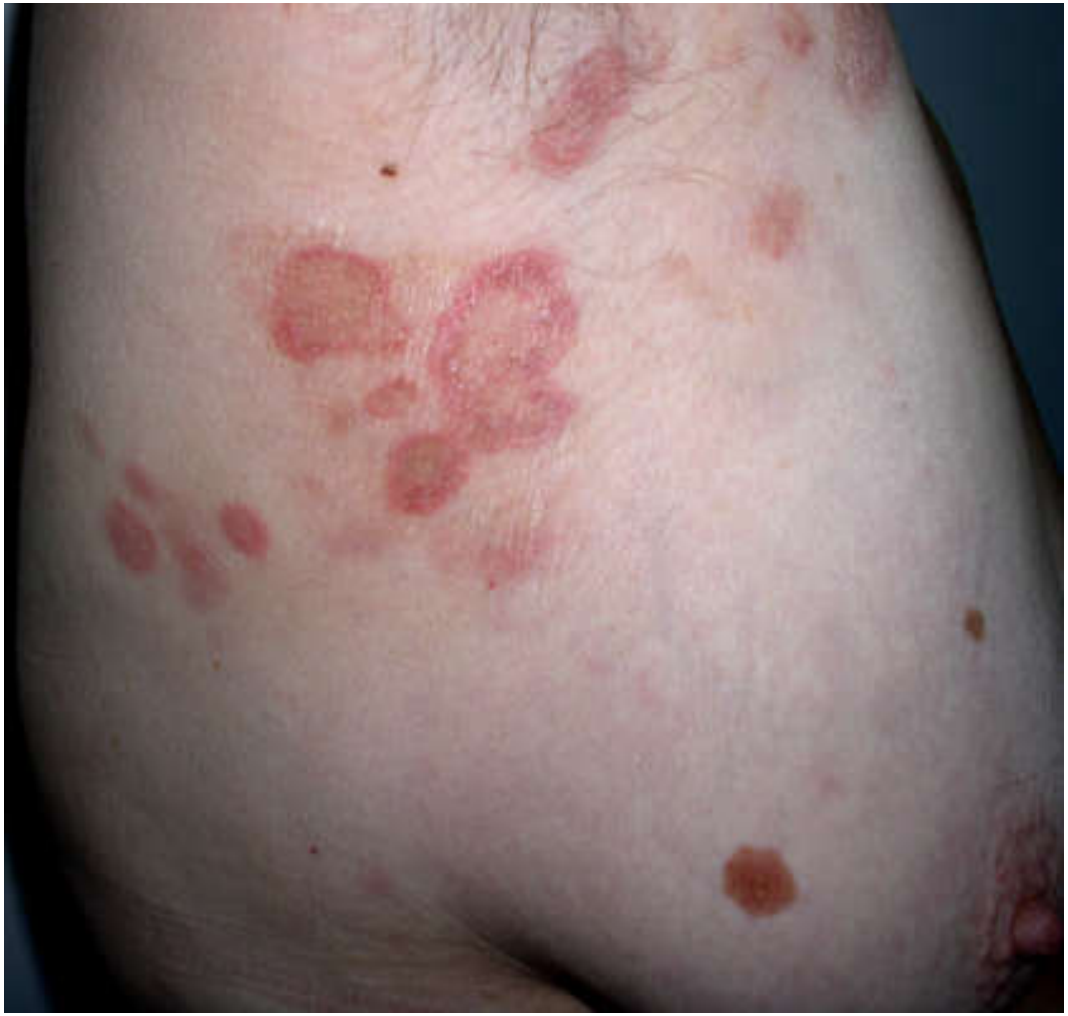
Clinical differentation of MF

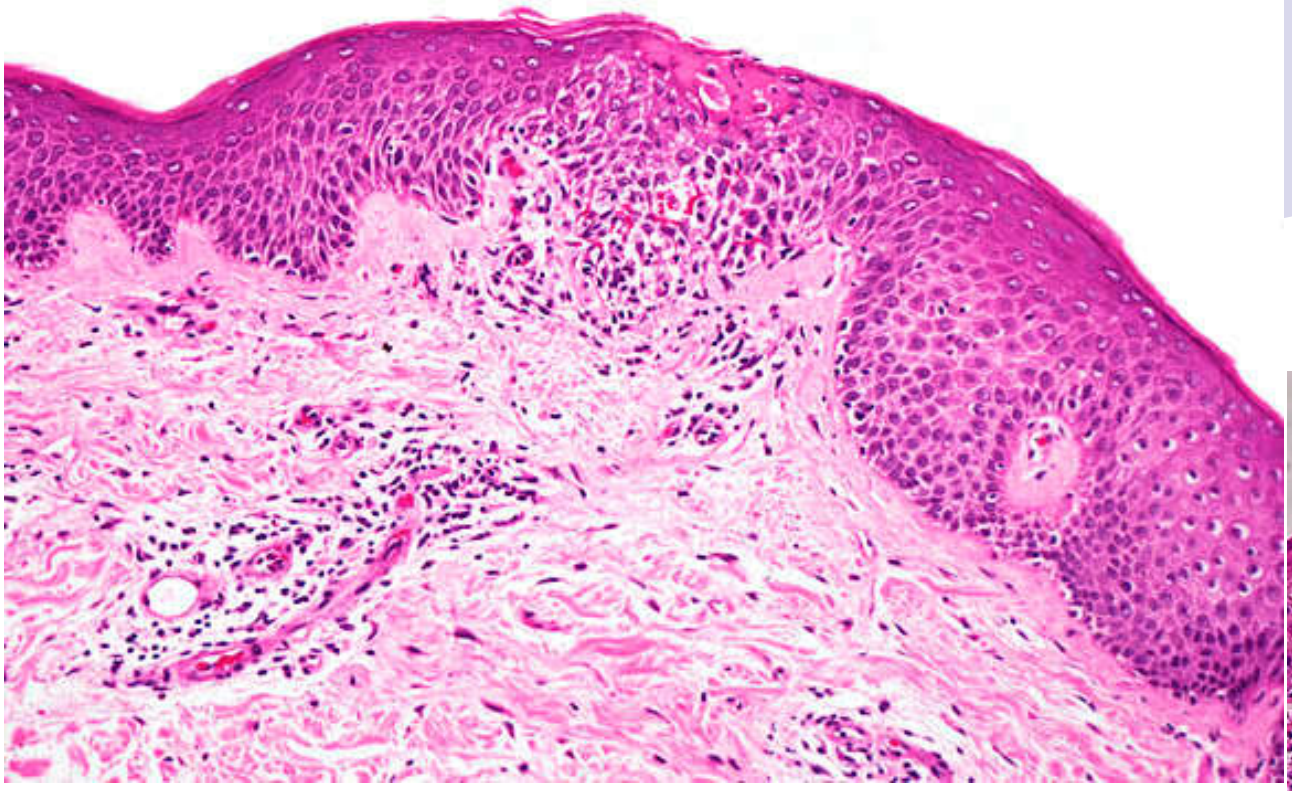
1. Atopic dermatitis
2. Allergic contact dermatitis
3. Irritated dermatitis
4. Psoriasis
5. Dermatophytosis
6. Chronic superficial lichenoid dermatitis
7. Morphea
8. Drug reactions (anticonvulsants: phenytoin, barbiturates, carbamazepine), atenolol, ACE inhibitors, allopurinol)



Eczema vs mycosis fungoides

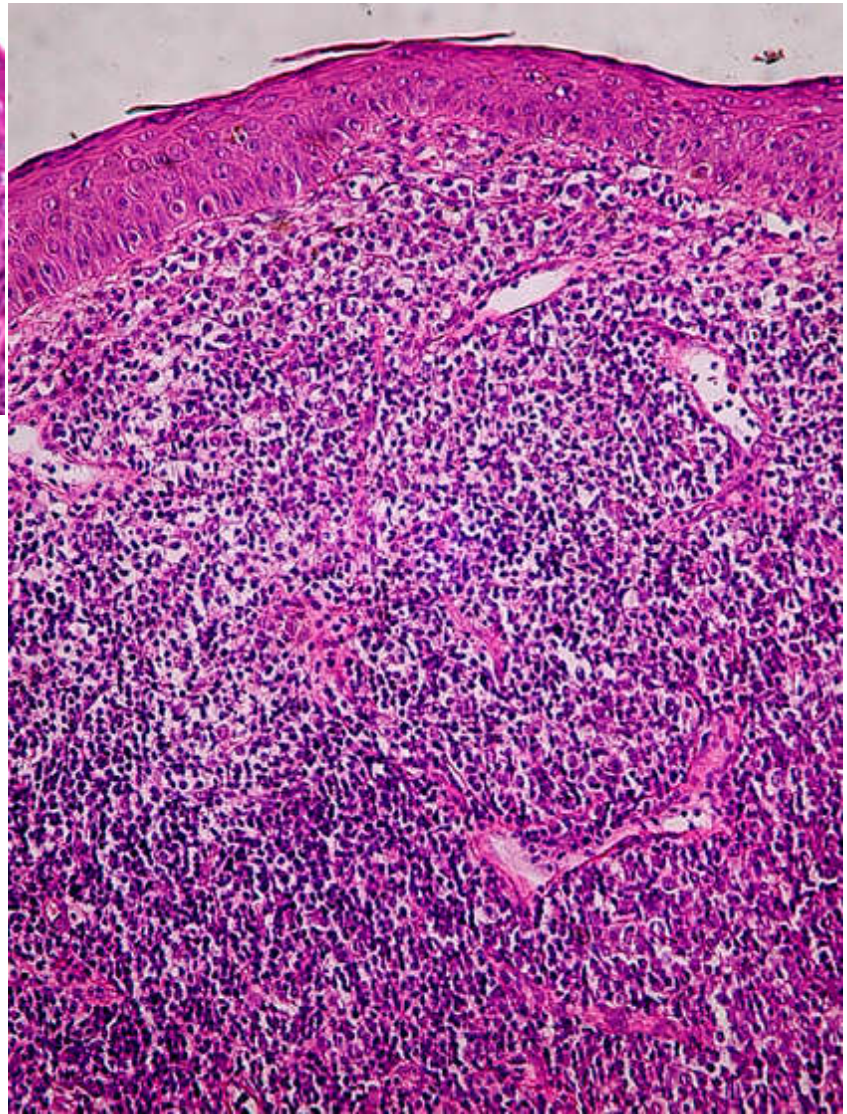




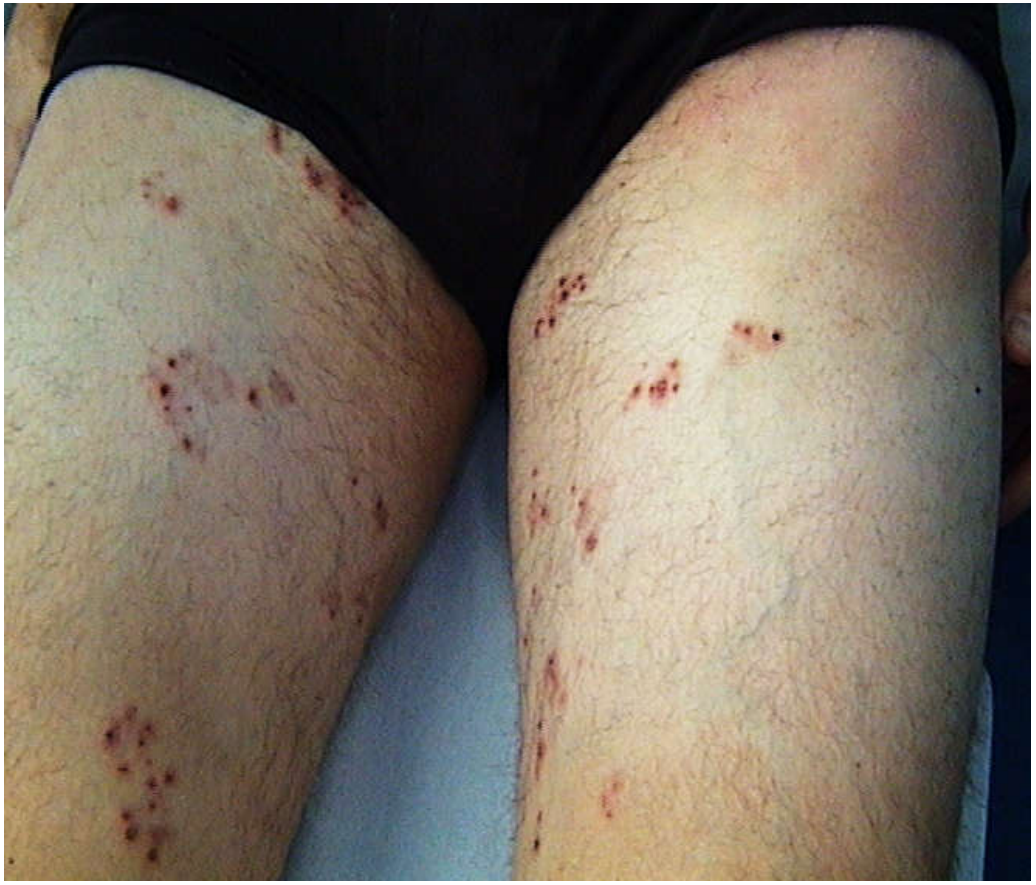


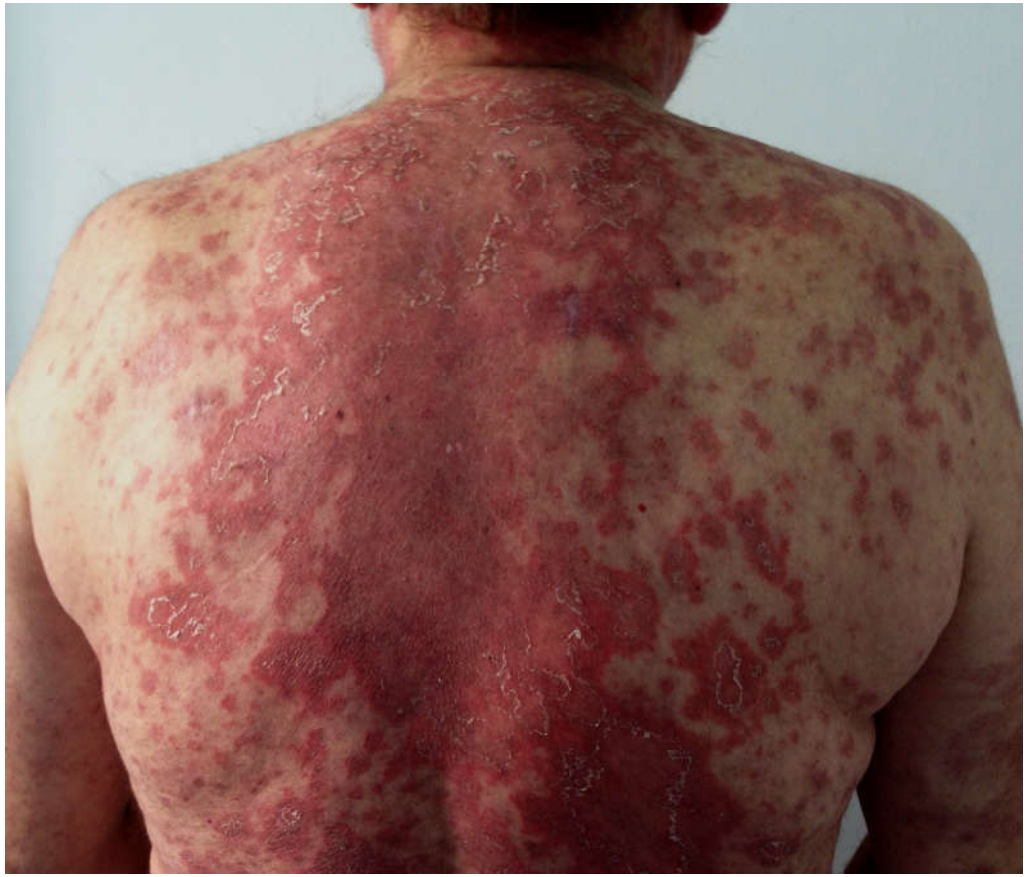
Allergic contact dermatitis

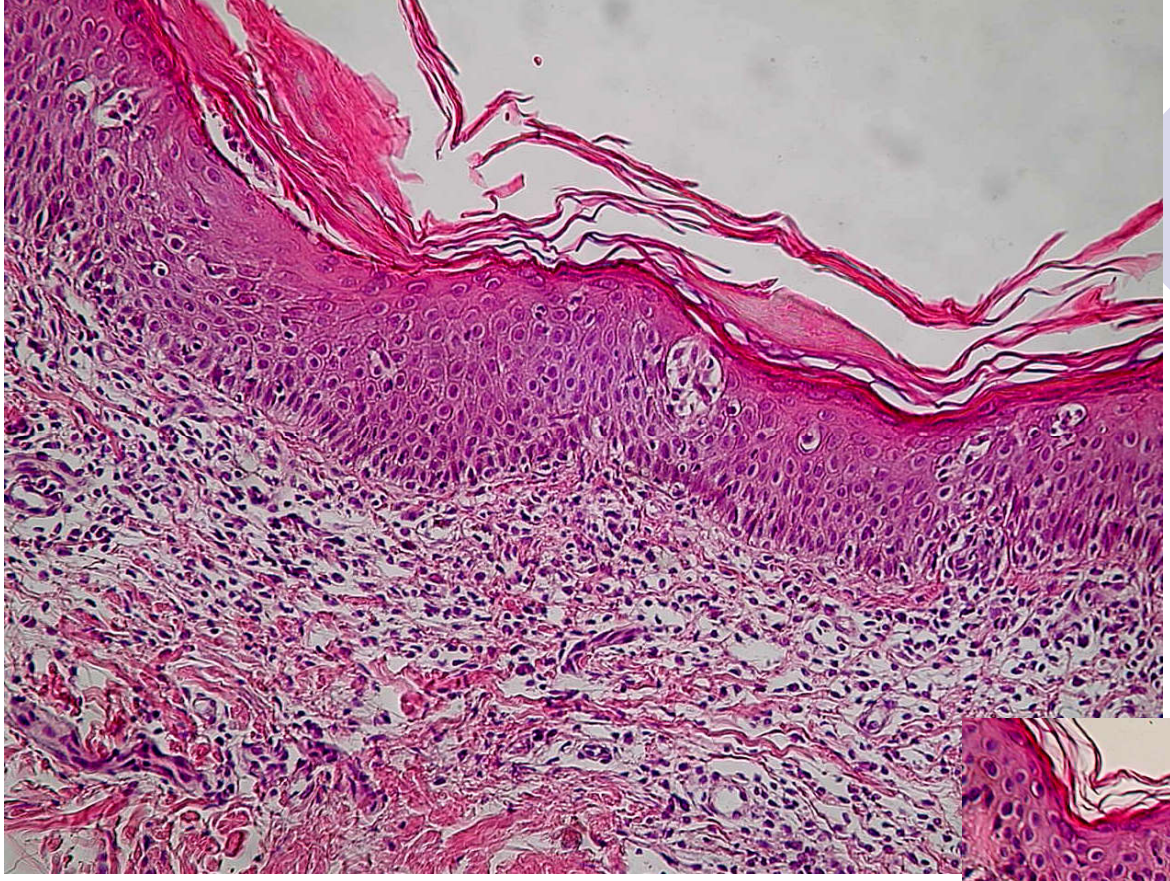
Mycosis fungoides



Mycosis fungoides vs subacute cutaneous lupus erythematosus

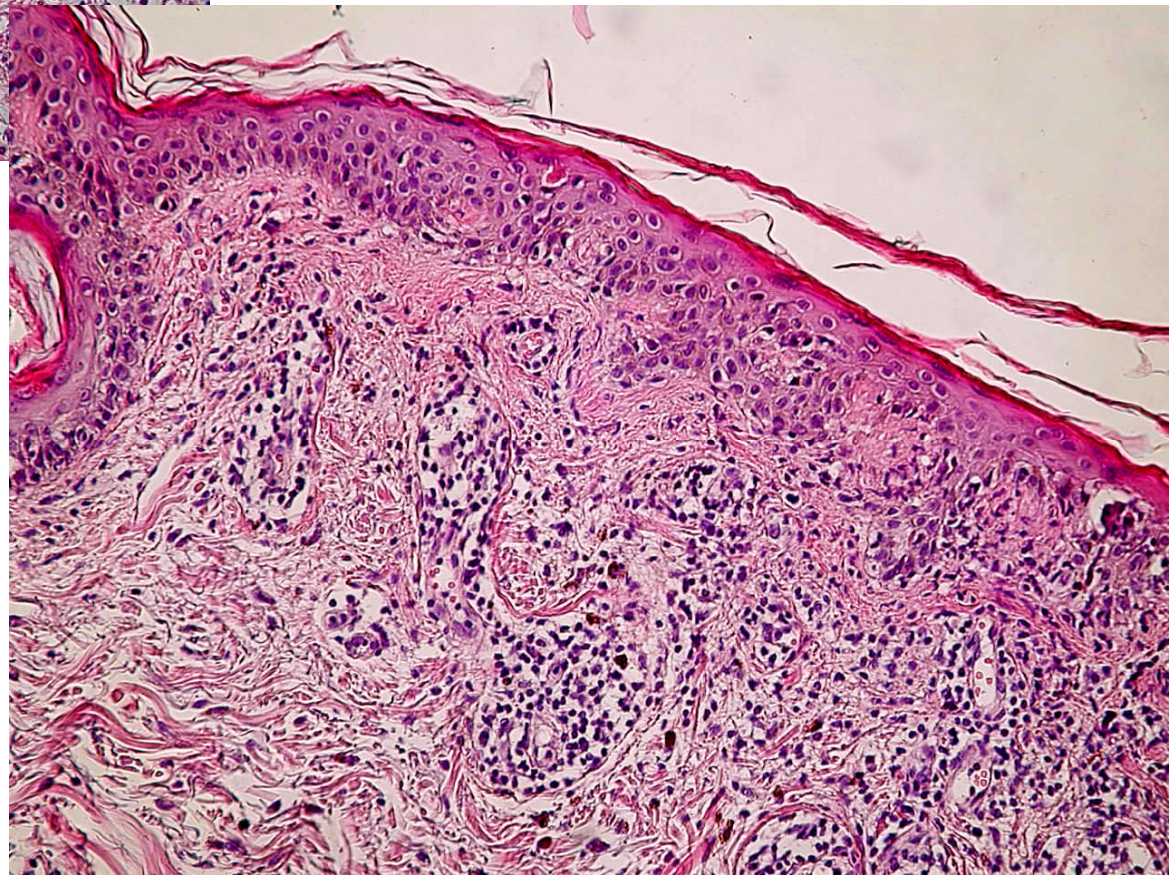




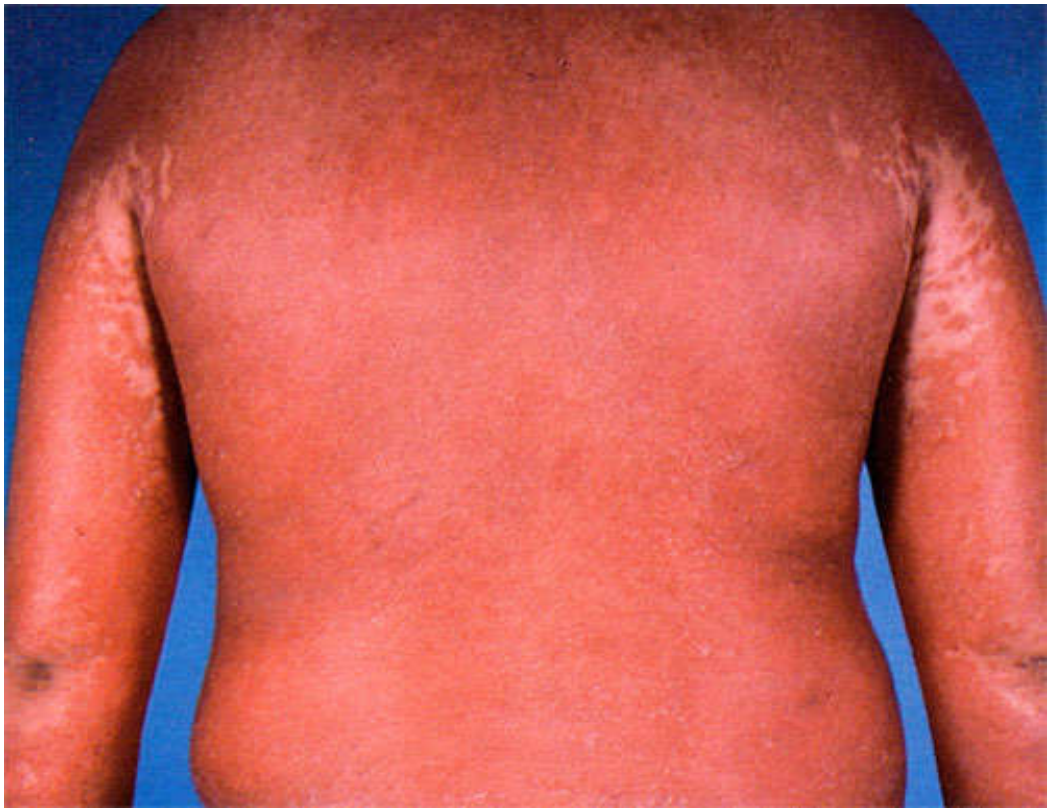


Lupus erythematosus

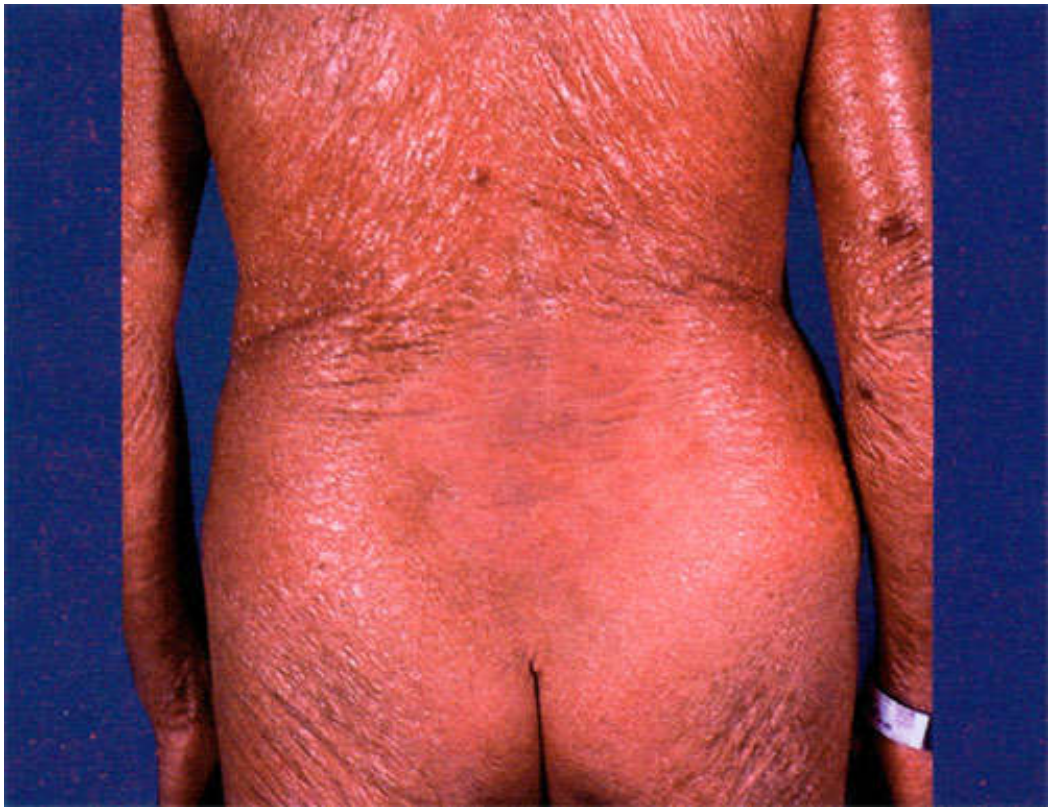
Mycosis fungoides



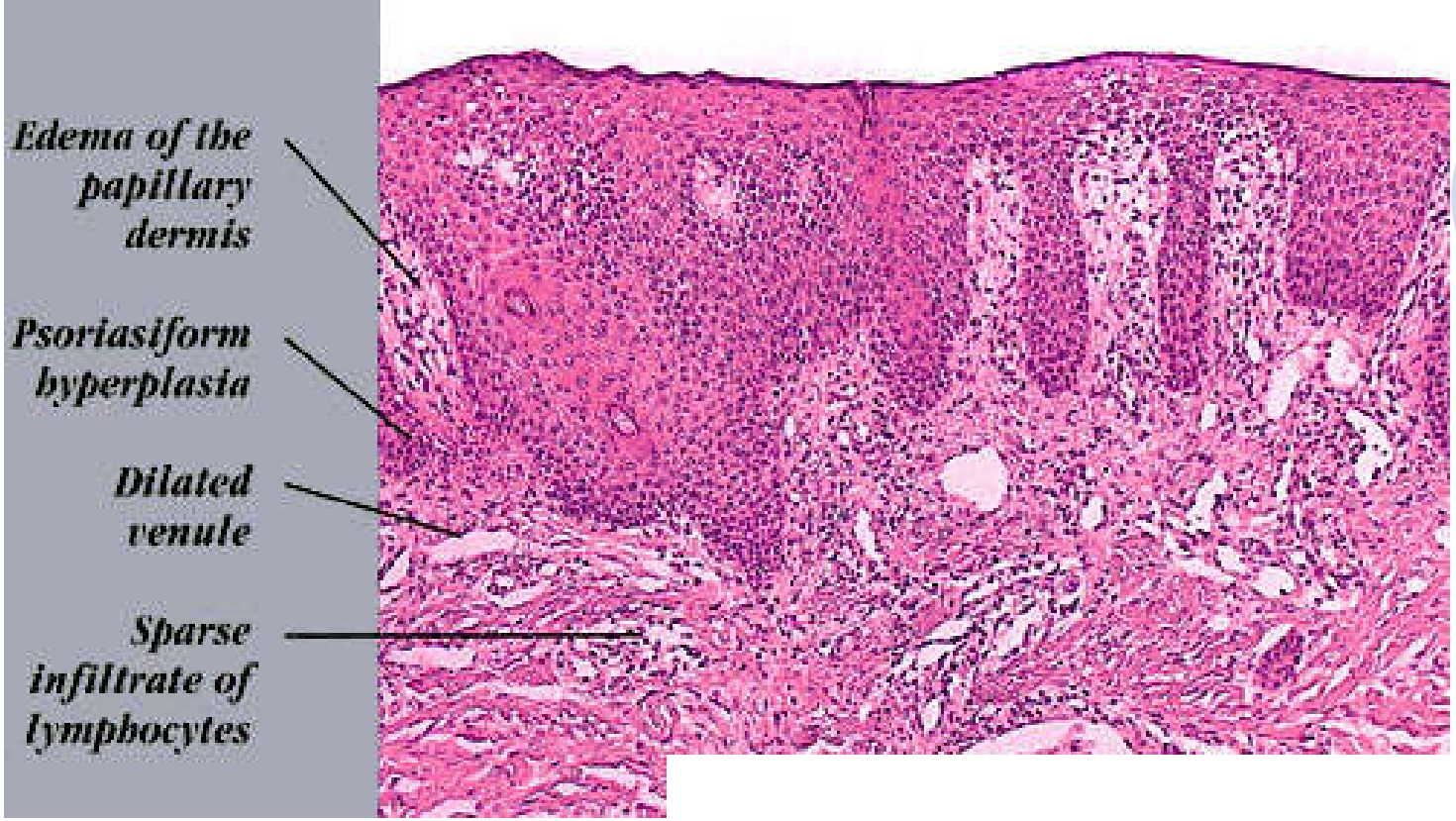
Erythroderma

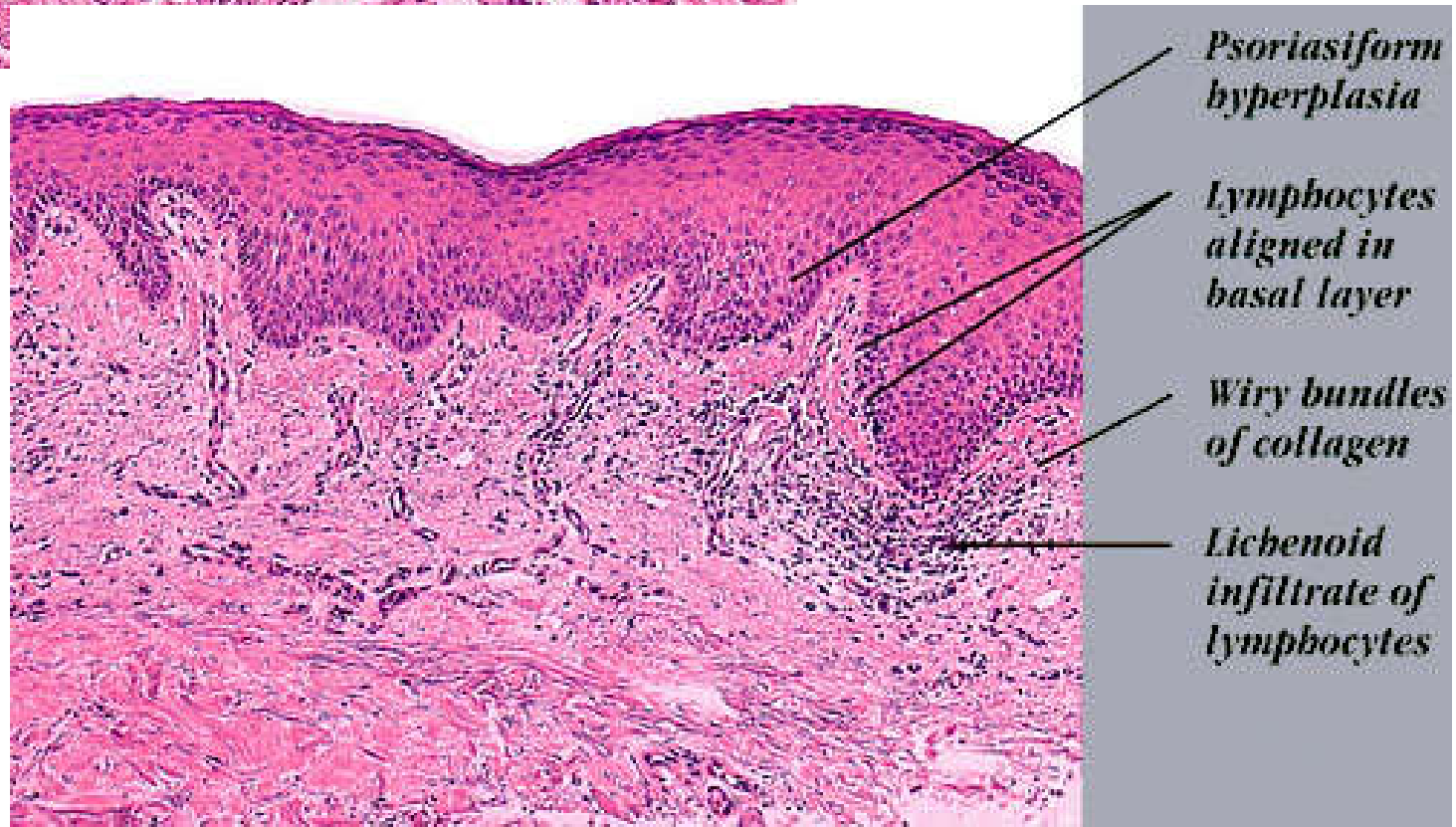


Psoriasis



Mycosis fungoides
(Cutaneous T cell lymphoma)

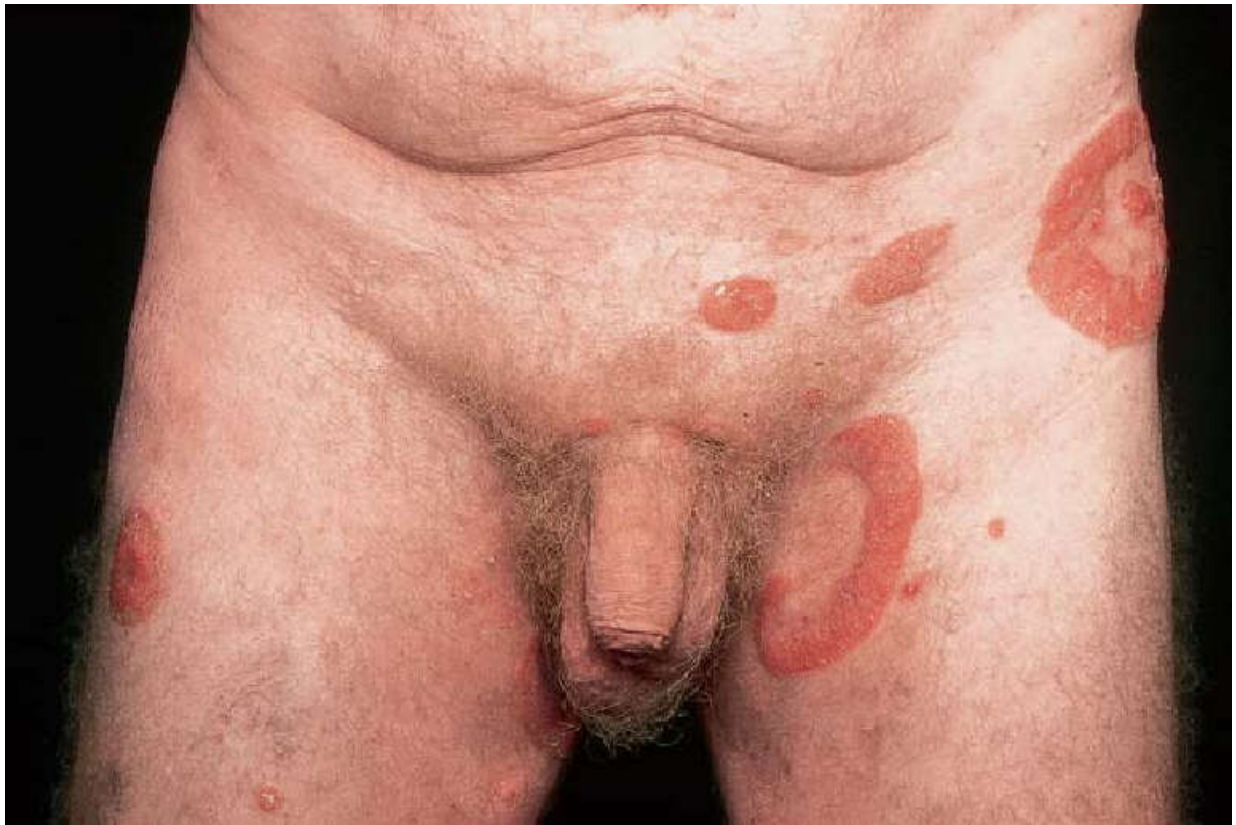

Edema of the papillary dermis
Psoriasiform hyperplasia
Dilated venule
Sparse infiltrate of lymphocytes


Psoriasiform hyperplasia
Lymphocytes aligned in basal layer
Wiry bundles of collagen
Lichenoid infiltrate of lymphocytes

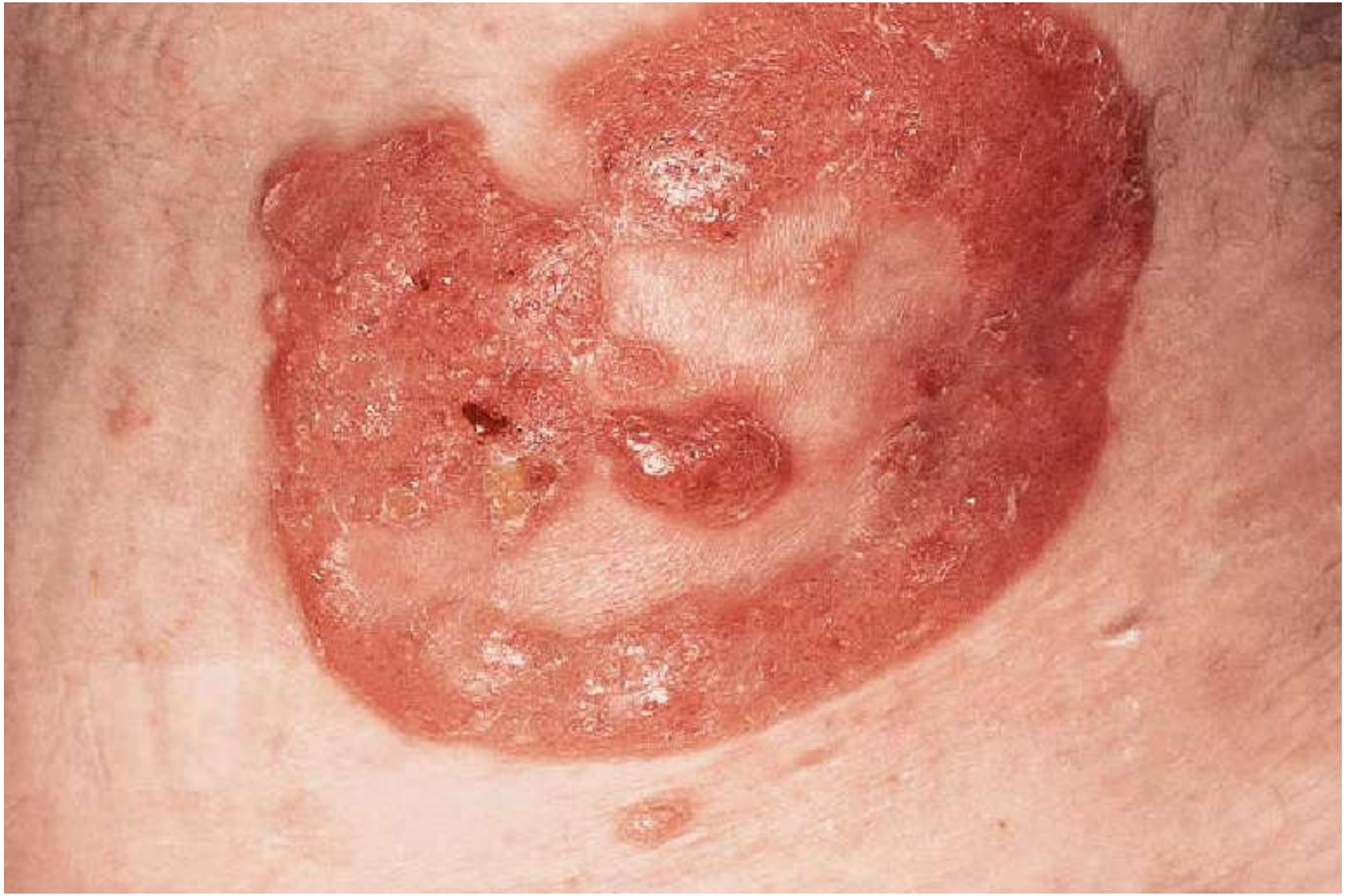
MF – plaque stage

- plaques are elevated, indurated, infiltrative, scaly, well demarcated
- annular, oval, kidney-shaped erythematous, reddish-brown plaques
- shape: annular, arcuate, serpiginous
- pruritus +++
- median survival

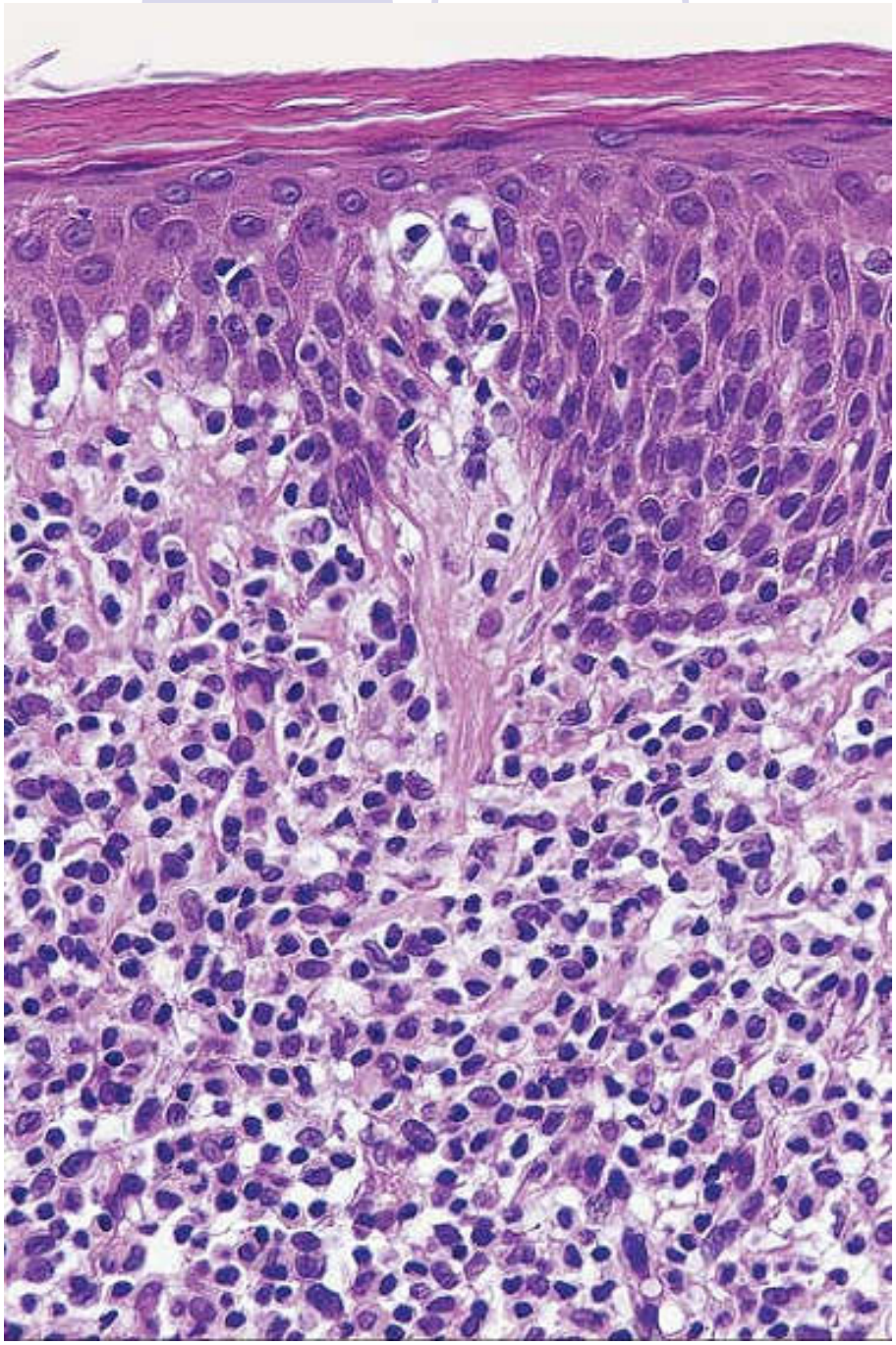
for person with patch- and plaque-stage MF disease is 12 years



Plaque of MF



Plaque MF in histology

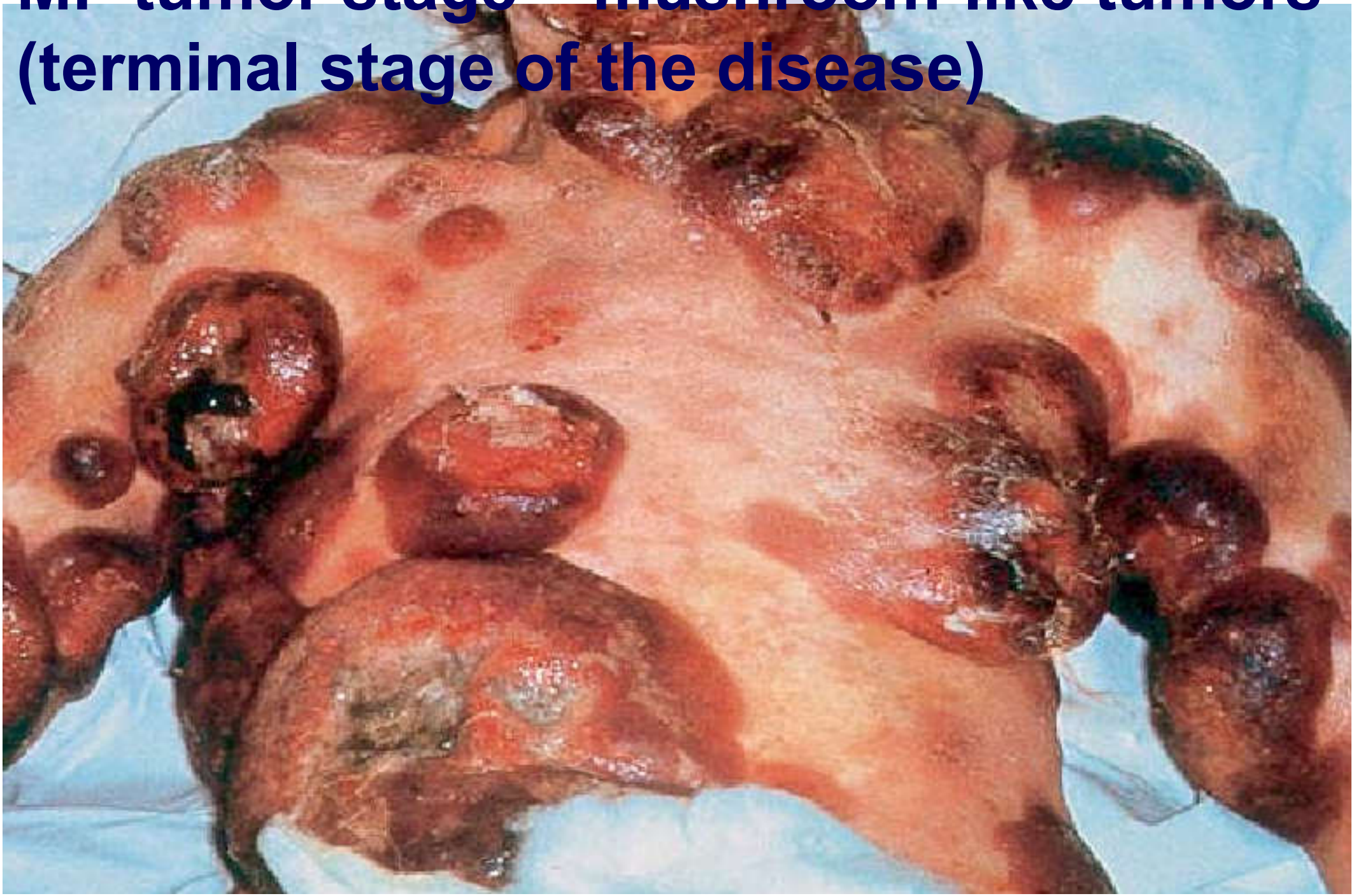


- epidermotropism is less pronounced
- dense band-like lichenoid infiltrate
- lymphocytes with irregular convoluted nuclear membranes and hyperchromatic nuclei

Tumor stage of MF – clinical presentation

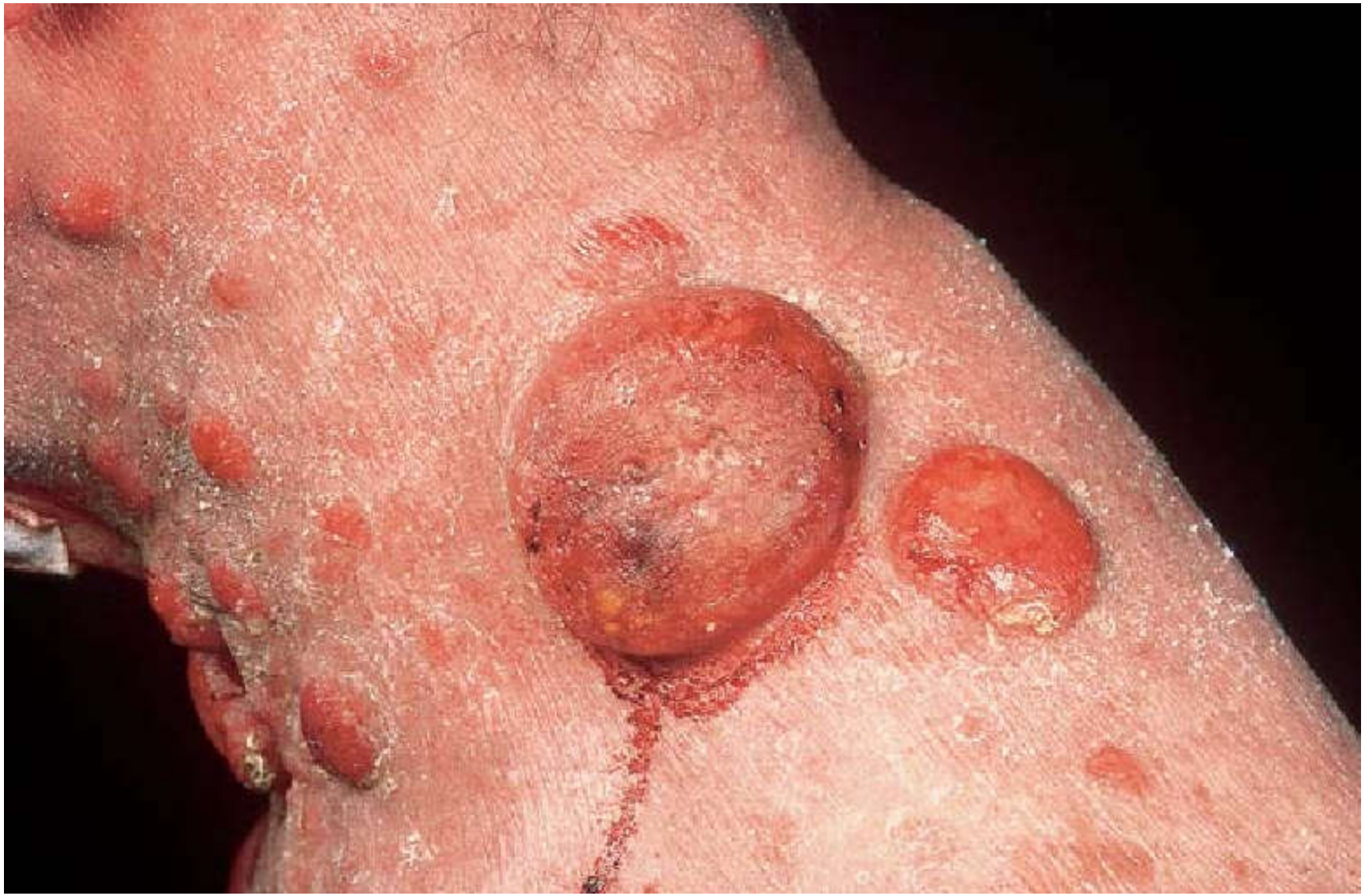
- last, terminal stage of MF
- tumors are present on the normal looking skin or on the base of the patches or plaques
- exaggerated vertical growth phase, resulting in large, reddish-brown or bluish-red smooth-surfaced nodules
- on the face – characteristic appearance called *facies leontina*
- the big smooth-surfaced nodules gave the resemblance to mushrooms – therefore fungoides (Alibert, 1806)
- visceral involvement (nodal, blood, spleen, liver, lungs, GI tract)

MF tumor stage – mushroom-like tumors (terminal stage of the disease)

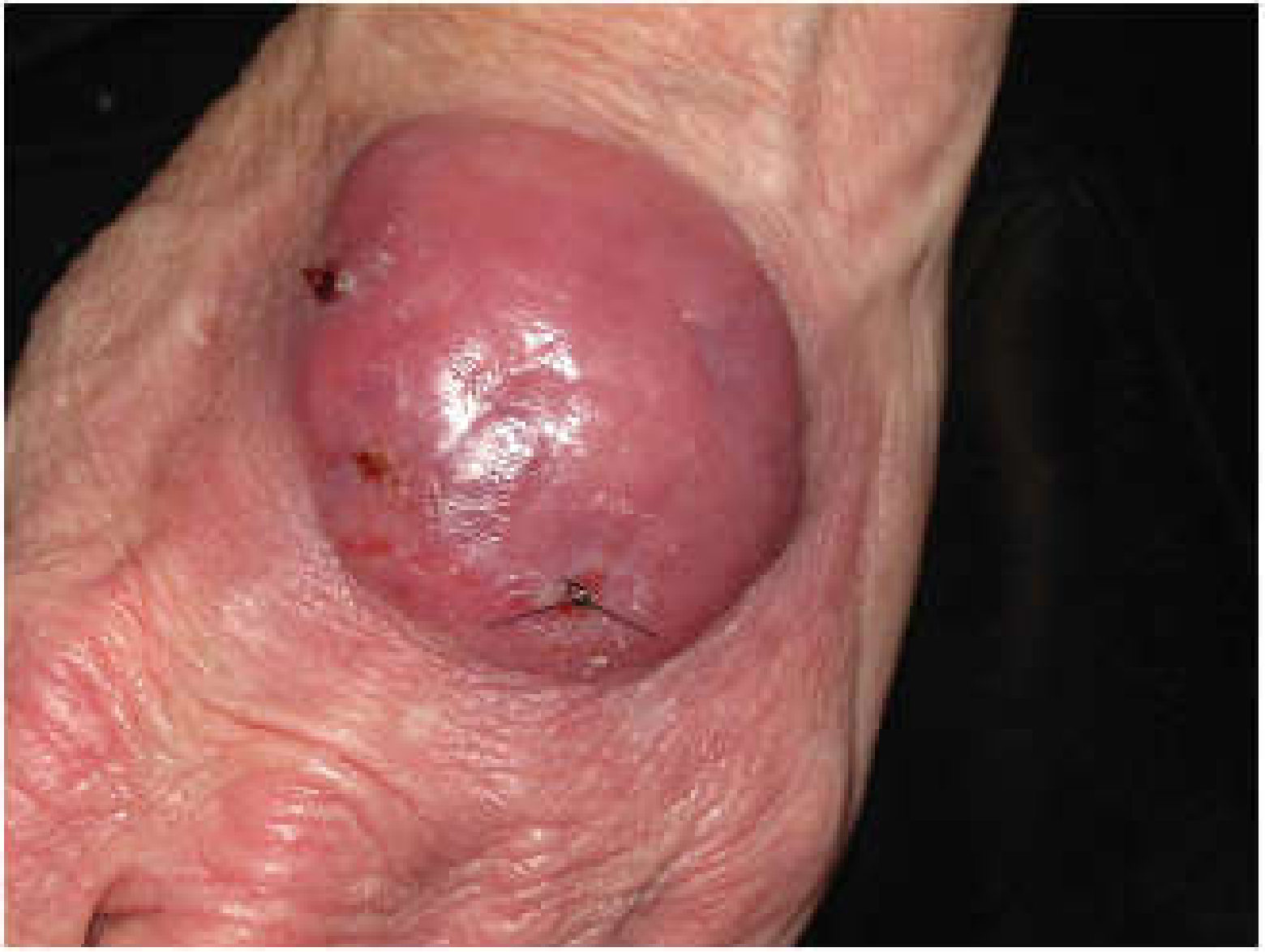


1806, Alibert

Nodular MF



Nodular MF



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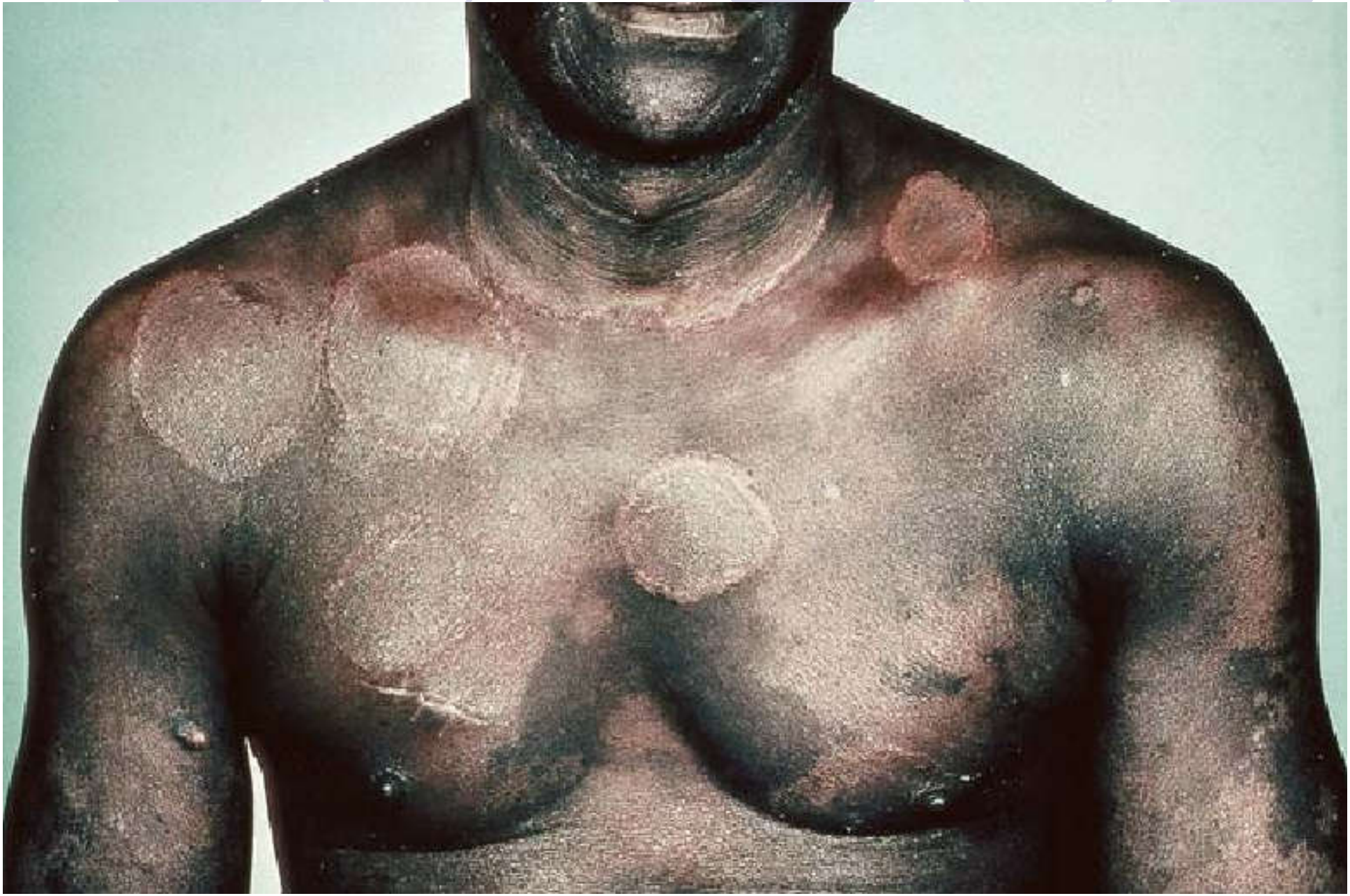
Types of mycosis fungoides

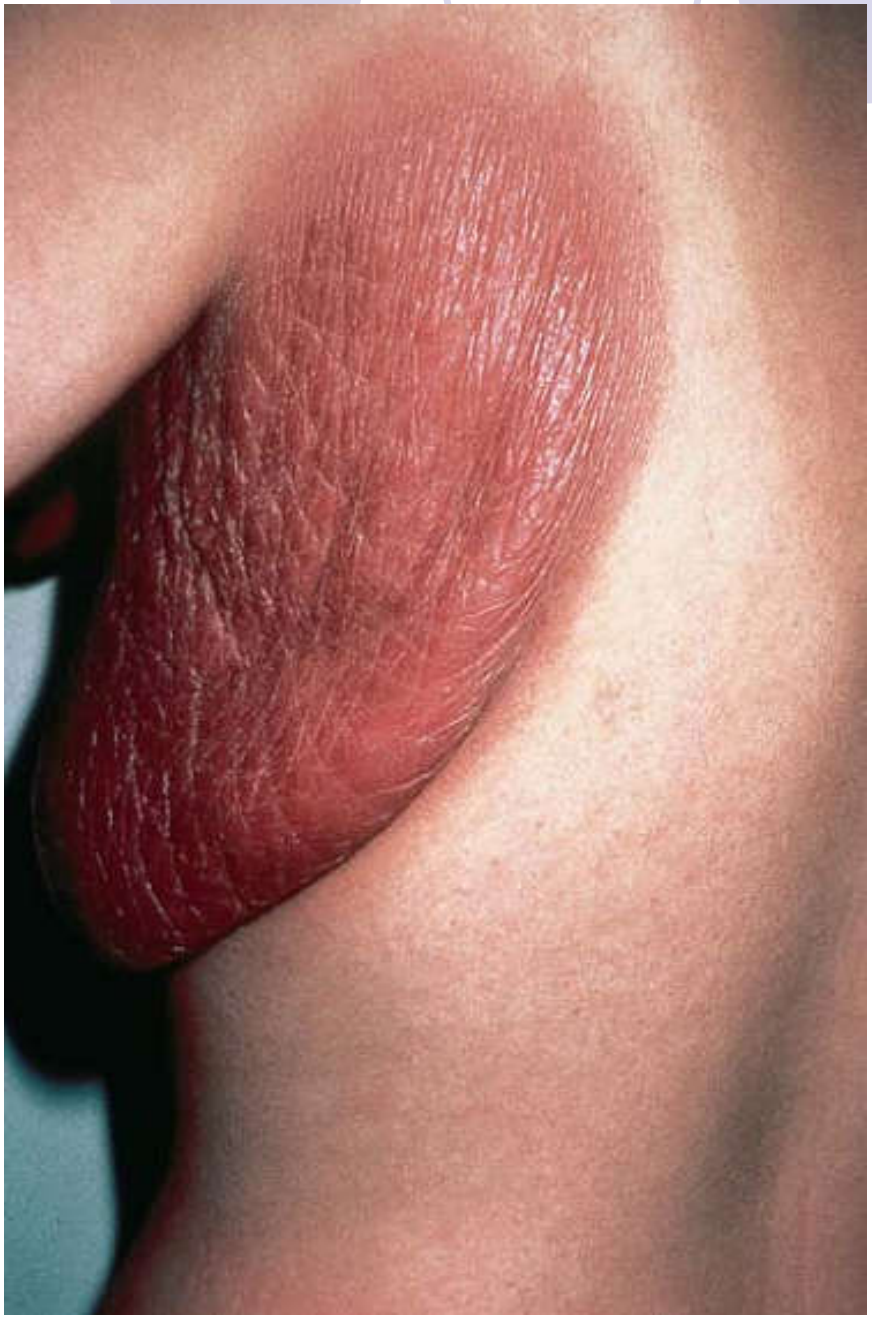
1. Erythrodermic
2. Hypopigmented
3. Folliculotropic
4. Syringotropic
5. Follicular mucinosis
6. Granulomatous slack skin
7. Pagetoid reticulosis

Hypopigmented MF

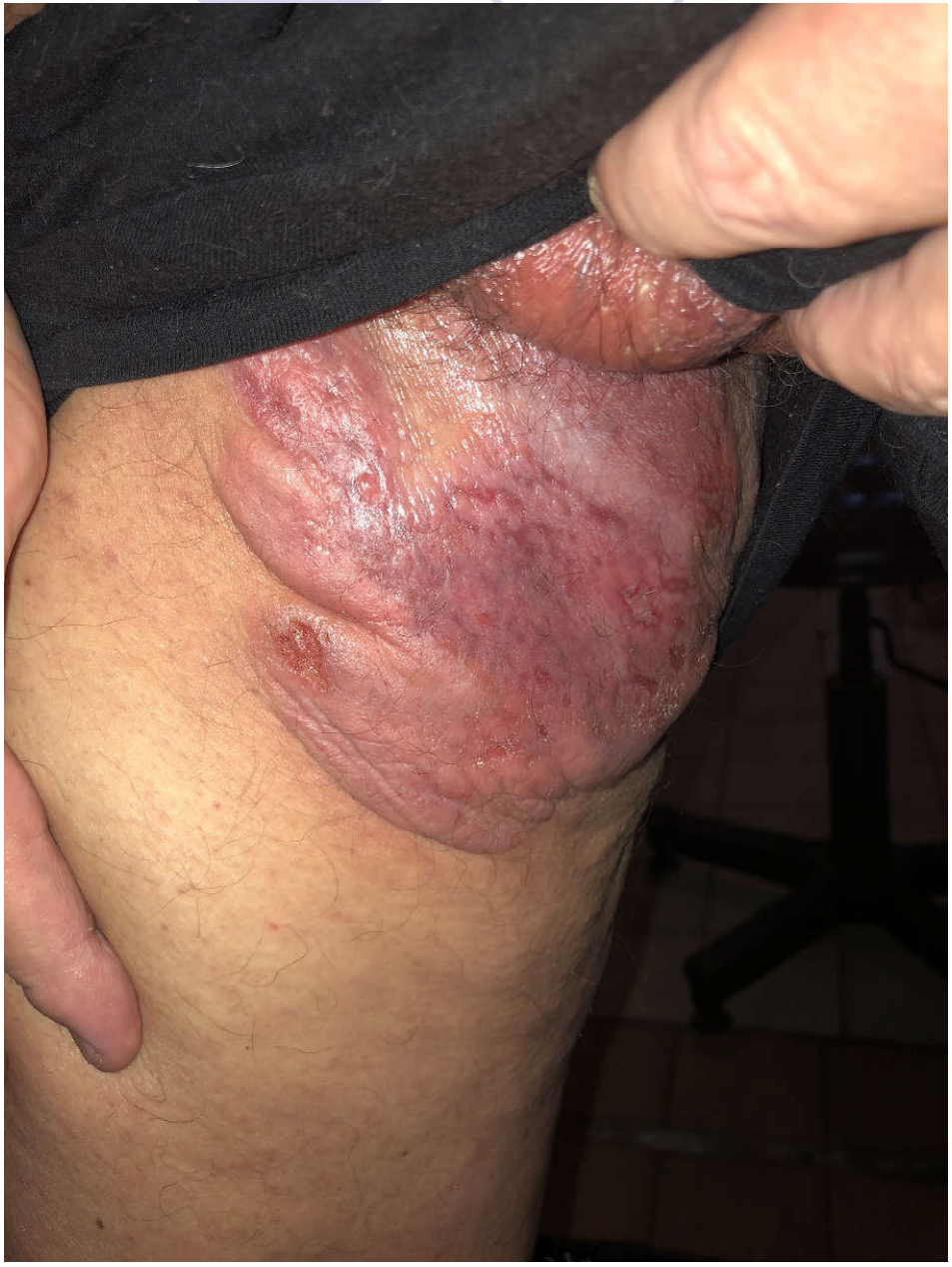


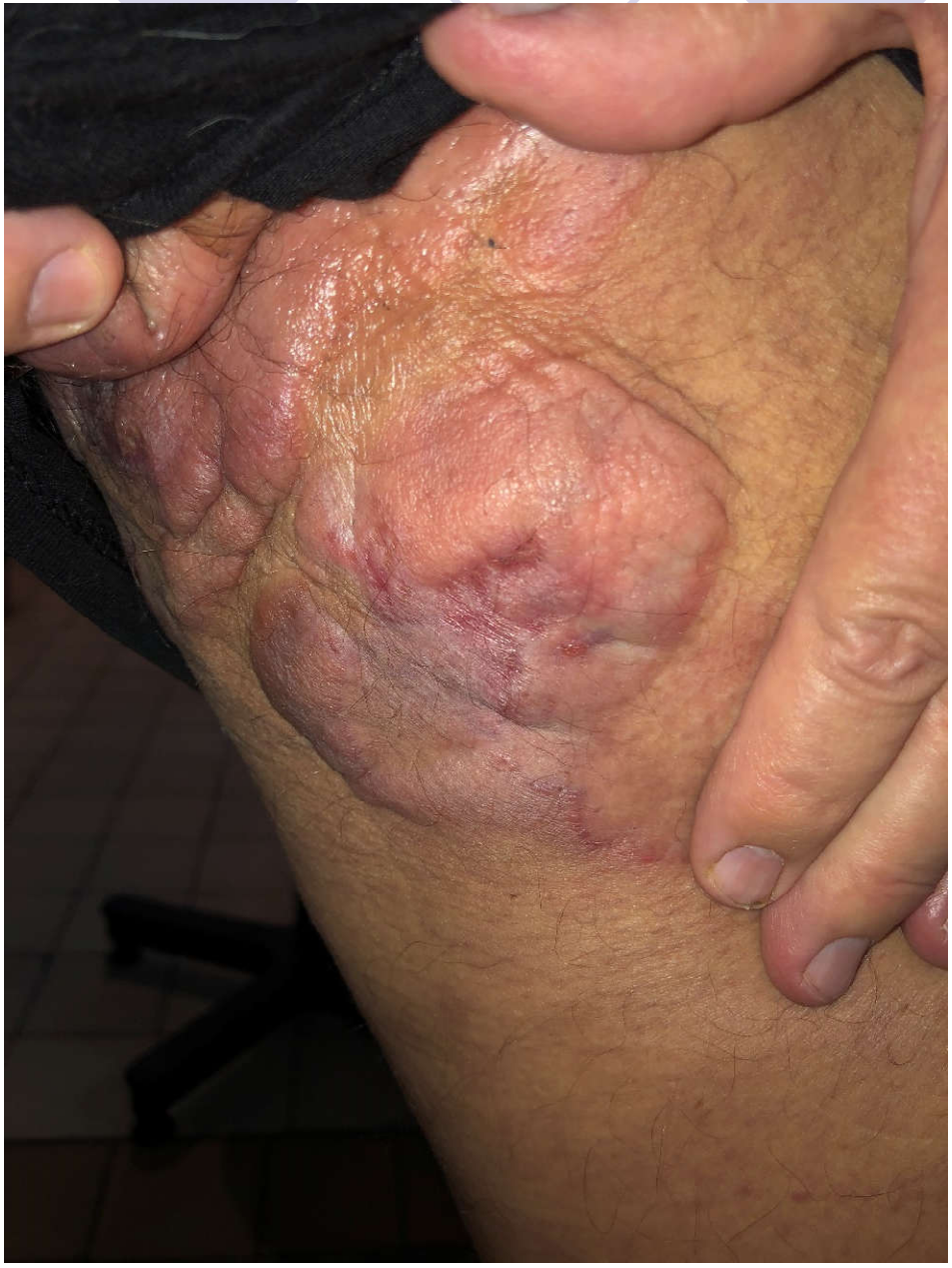
Granulomatous slack skin

- rare variant of MF
- affects folds and induces tremendous skin laxity
- in younger patients and more common in women
- dense diffuse granulomatous infiltrates composed of atypical lymphocytes and histiocytes

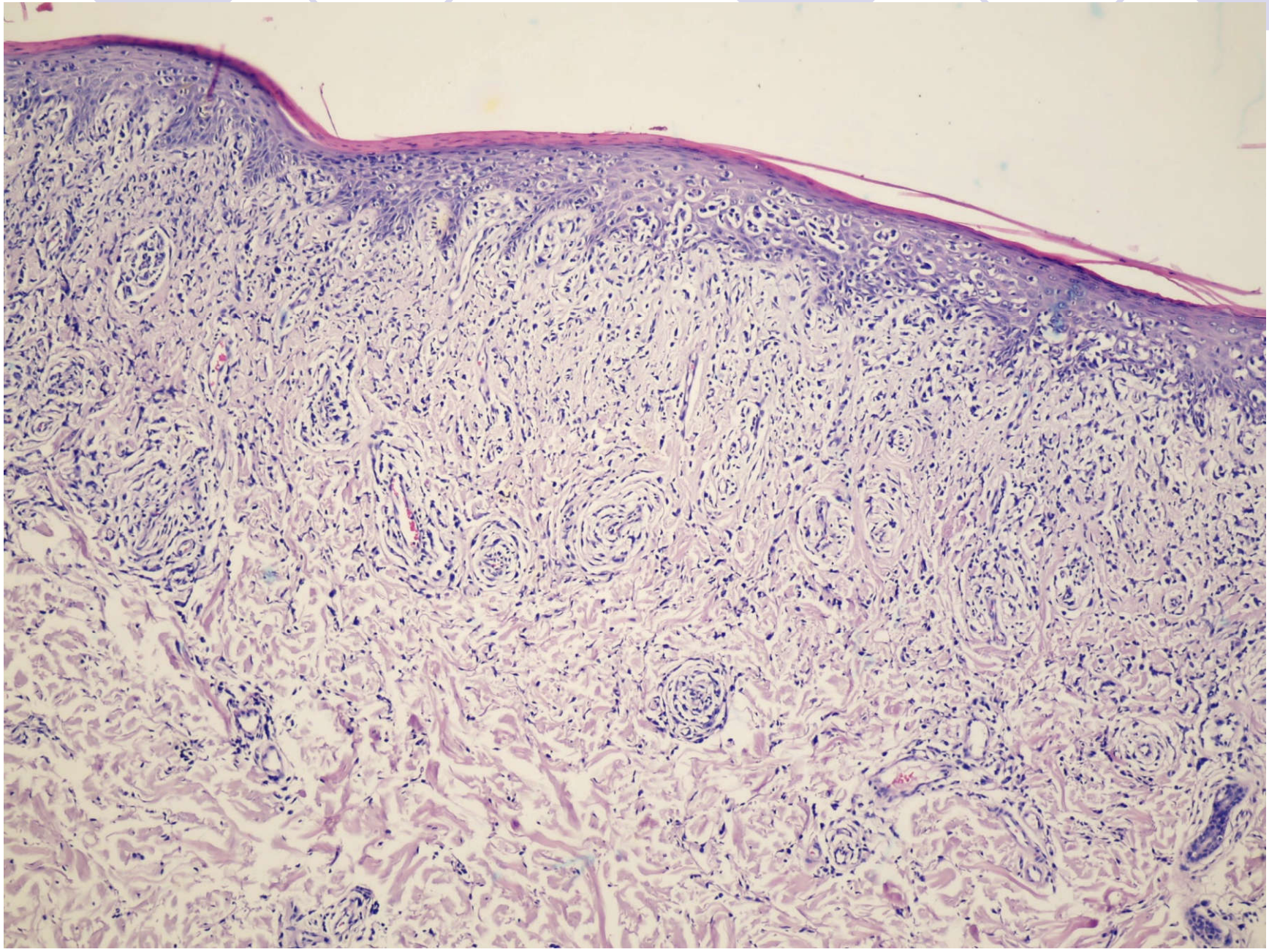


Granulomatous slack skin



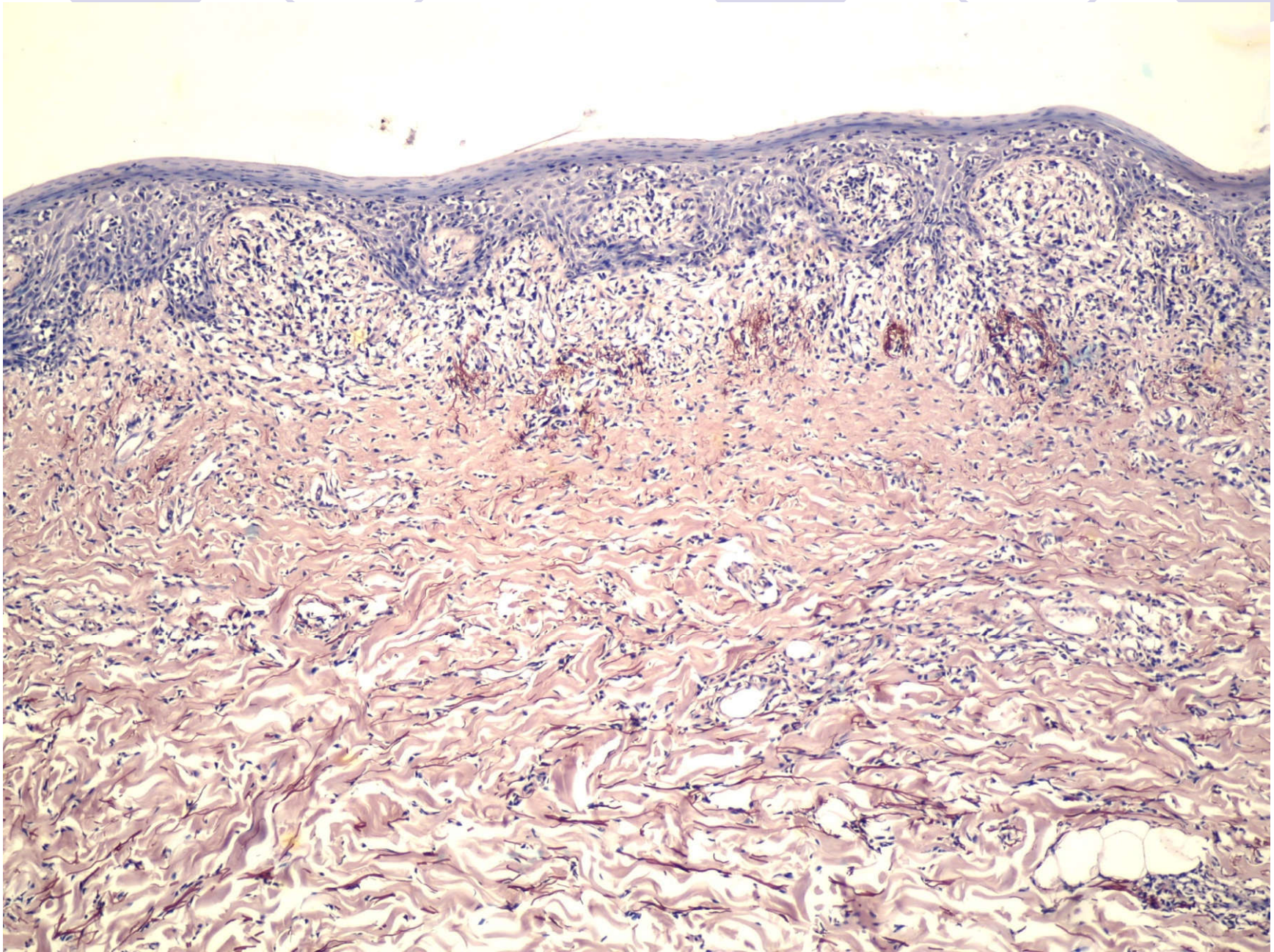


Granulomatous slack skin

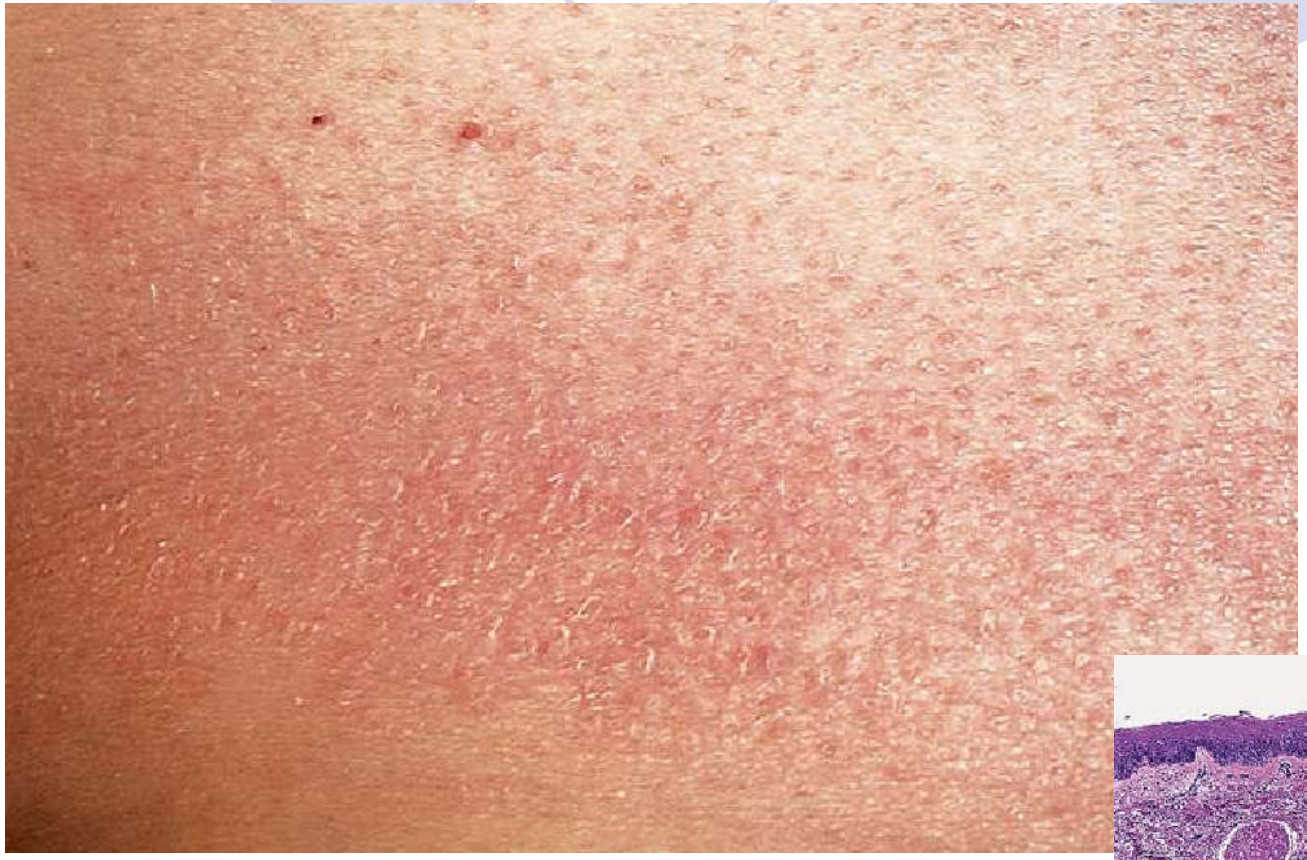


Granulomatous slack skin

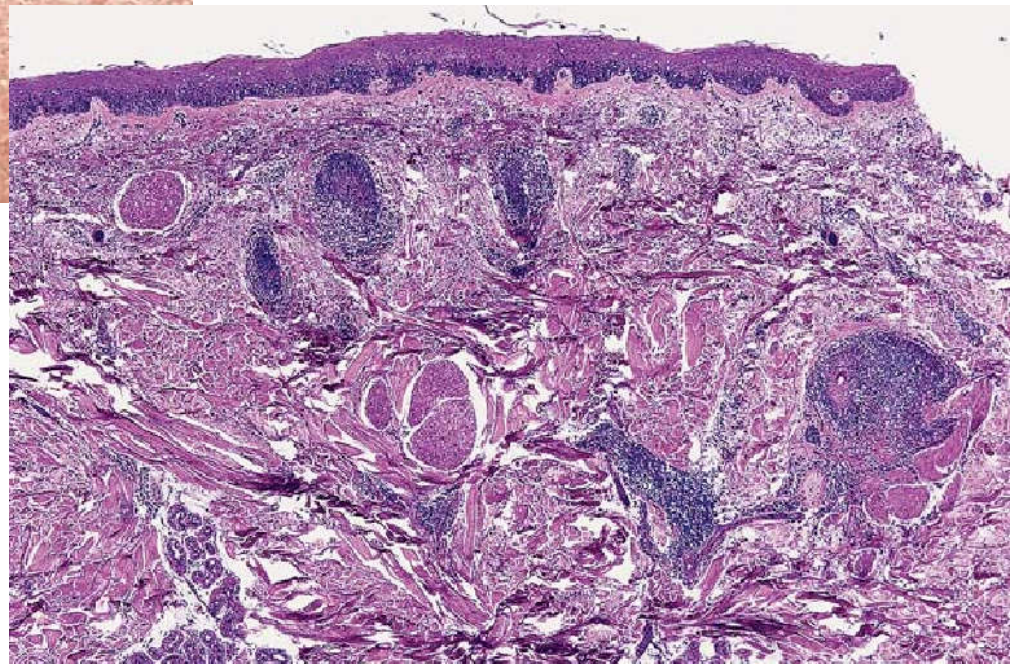
(orcein stain for elastin)

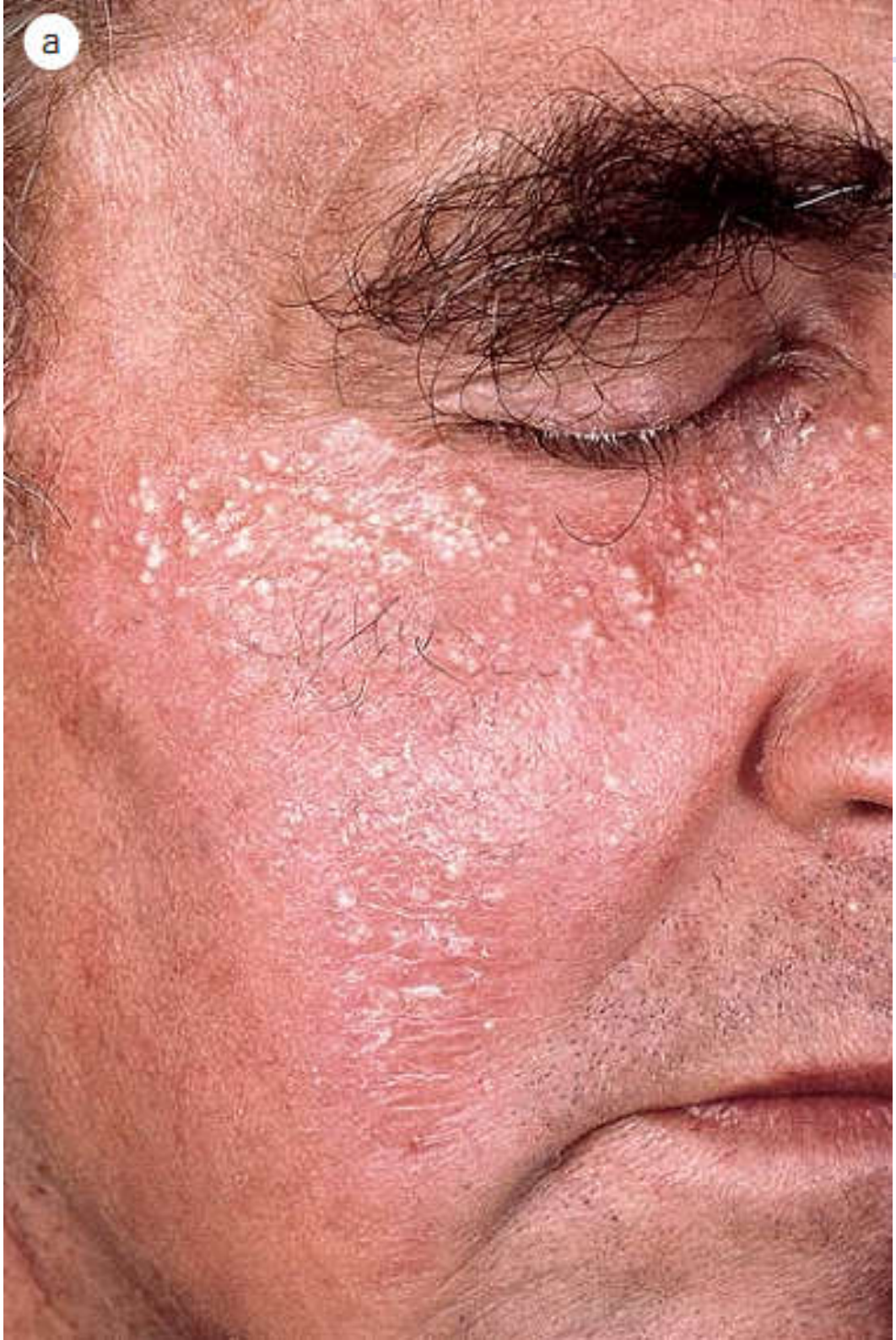


Folliculotropic MF



- head and neck
- permanent alopecia
- severe pruritus

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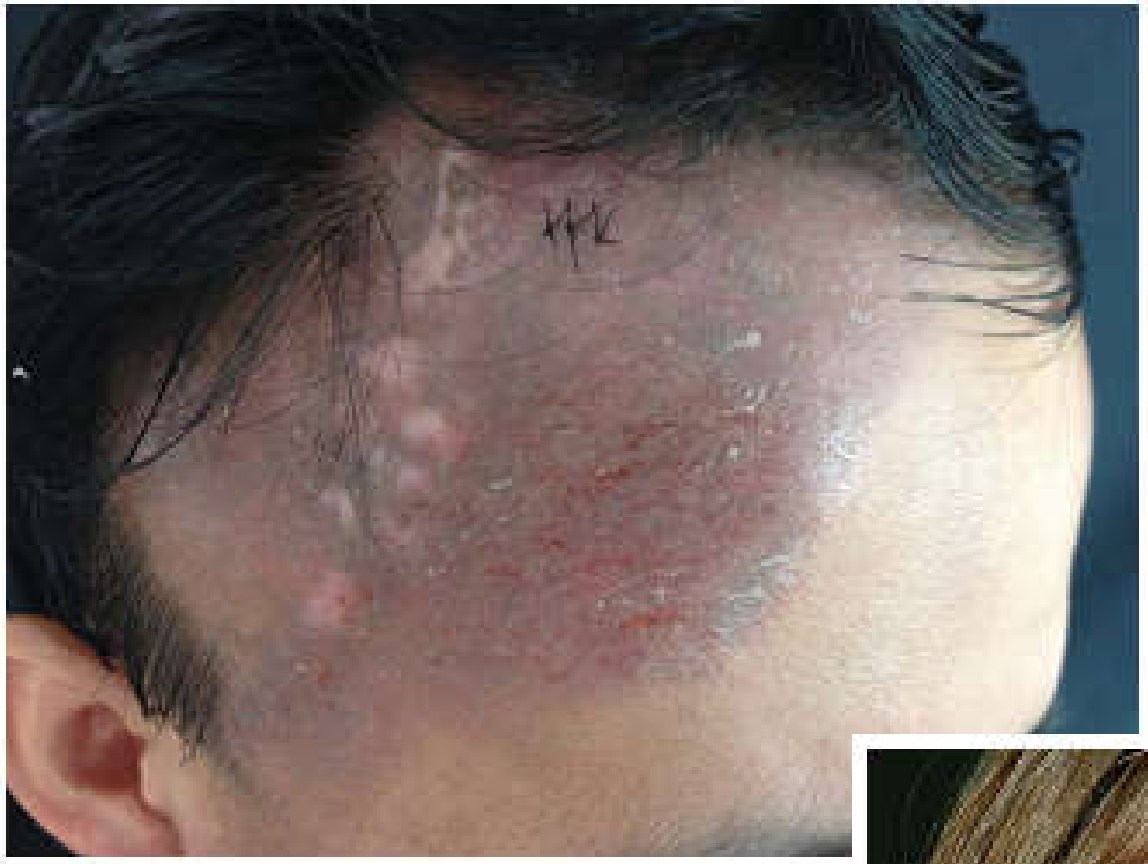
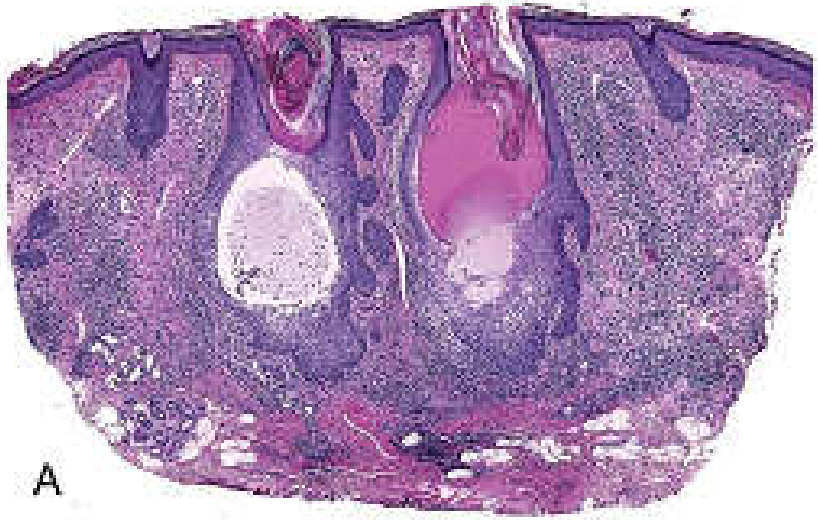
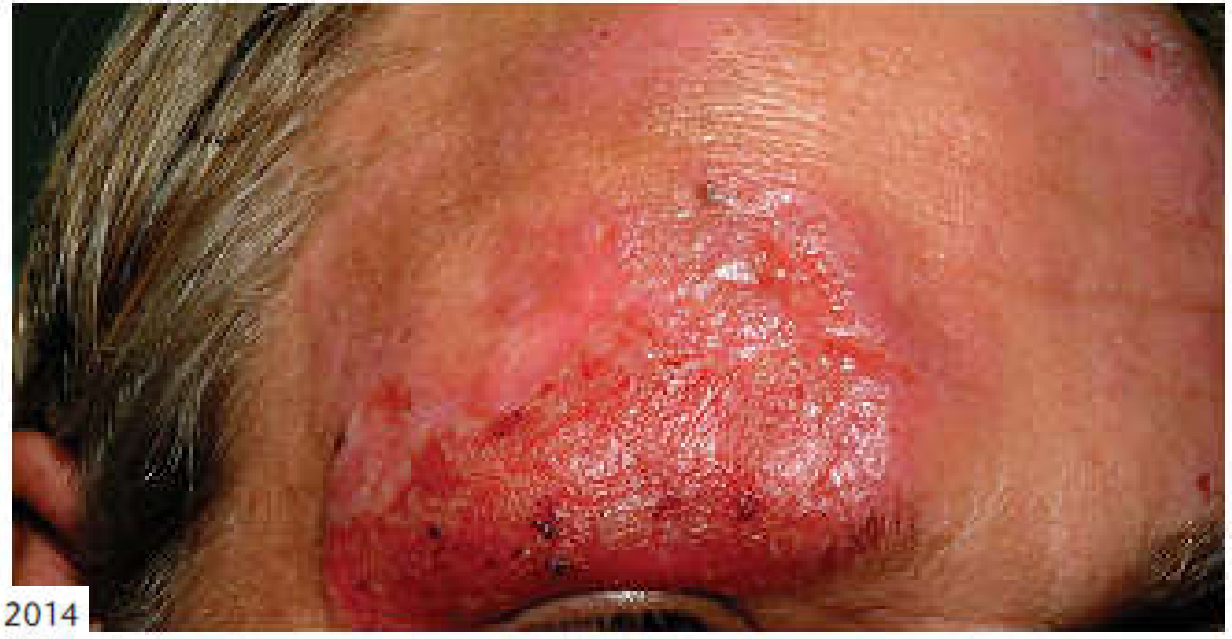
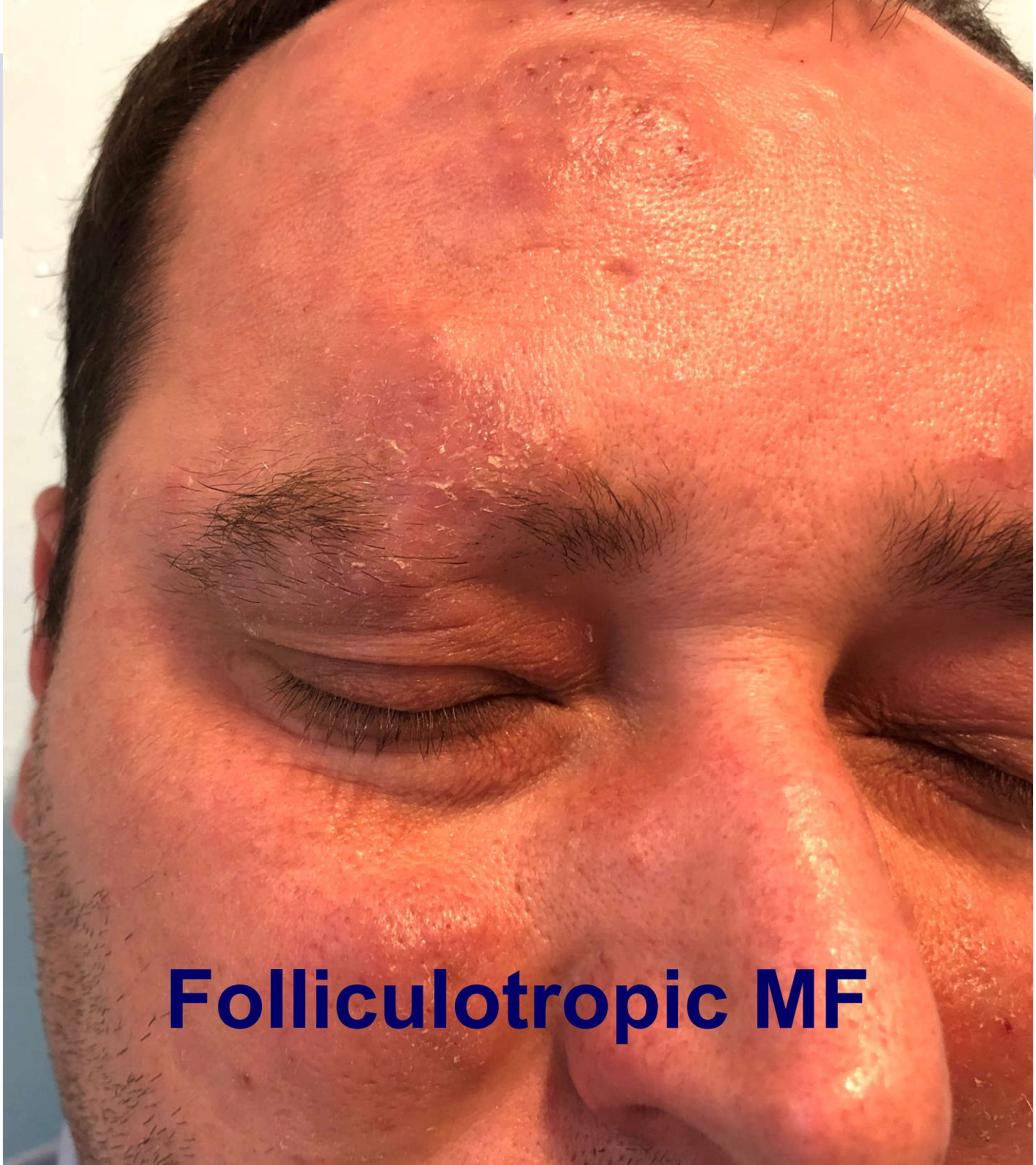
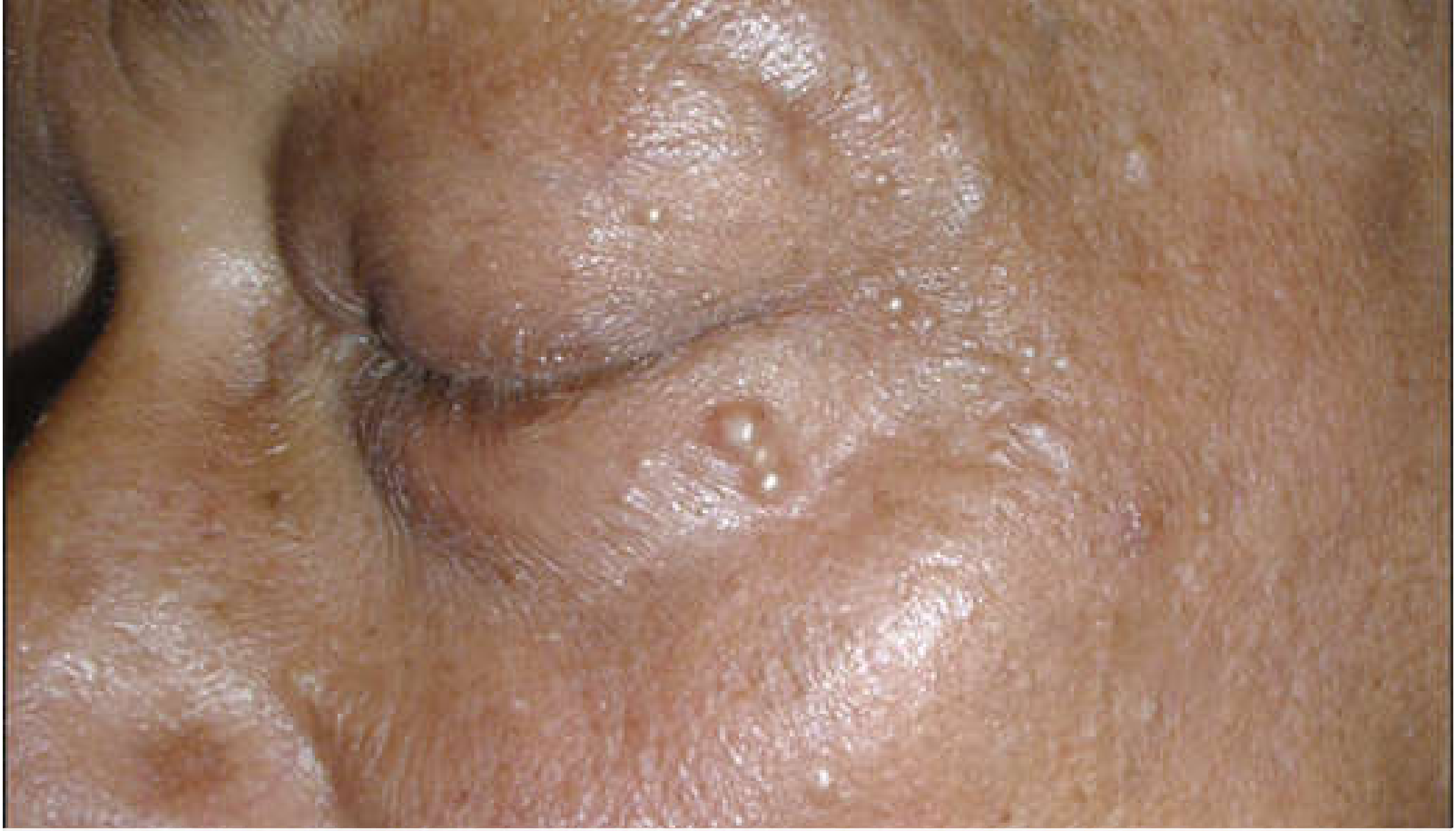
Folliculotropic MF







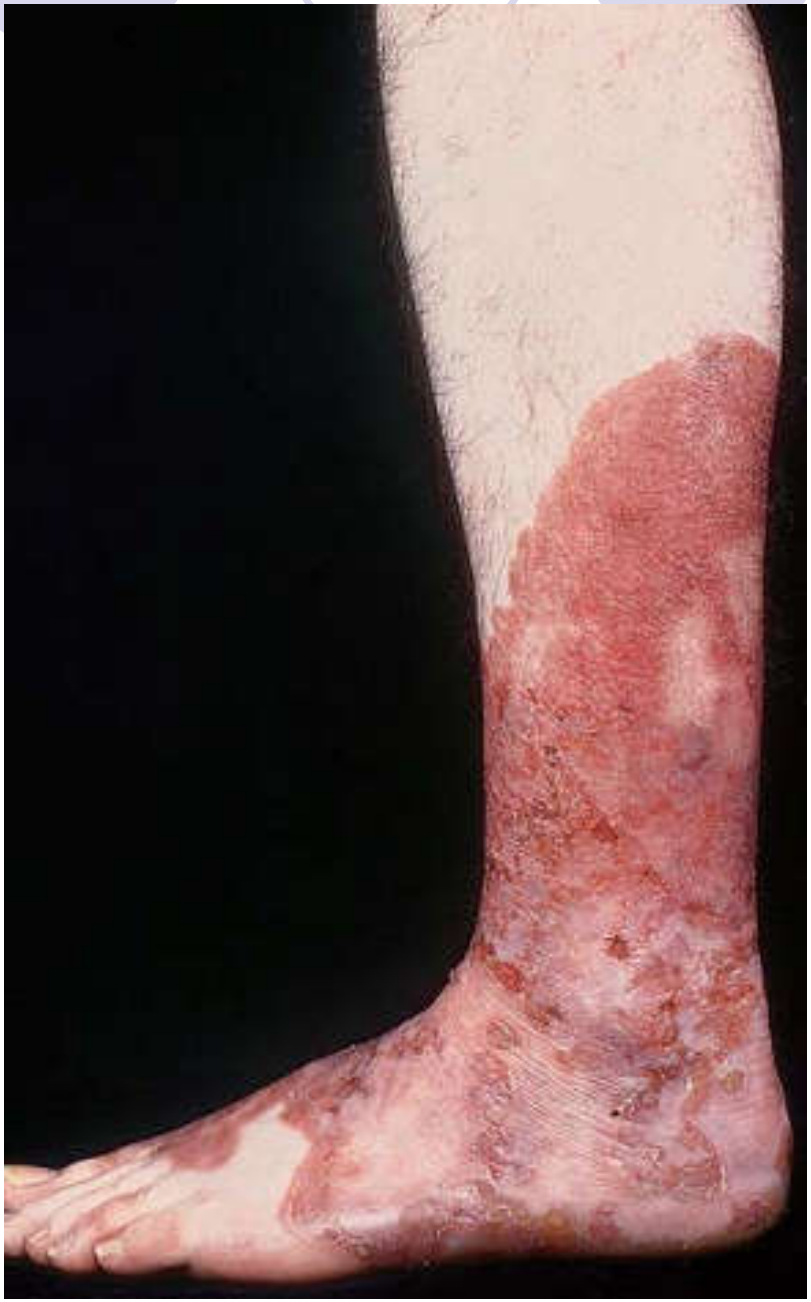

Folliculotropic MF



Syringotropic mycosis fungoides

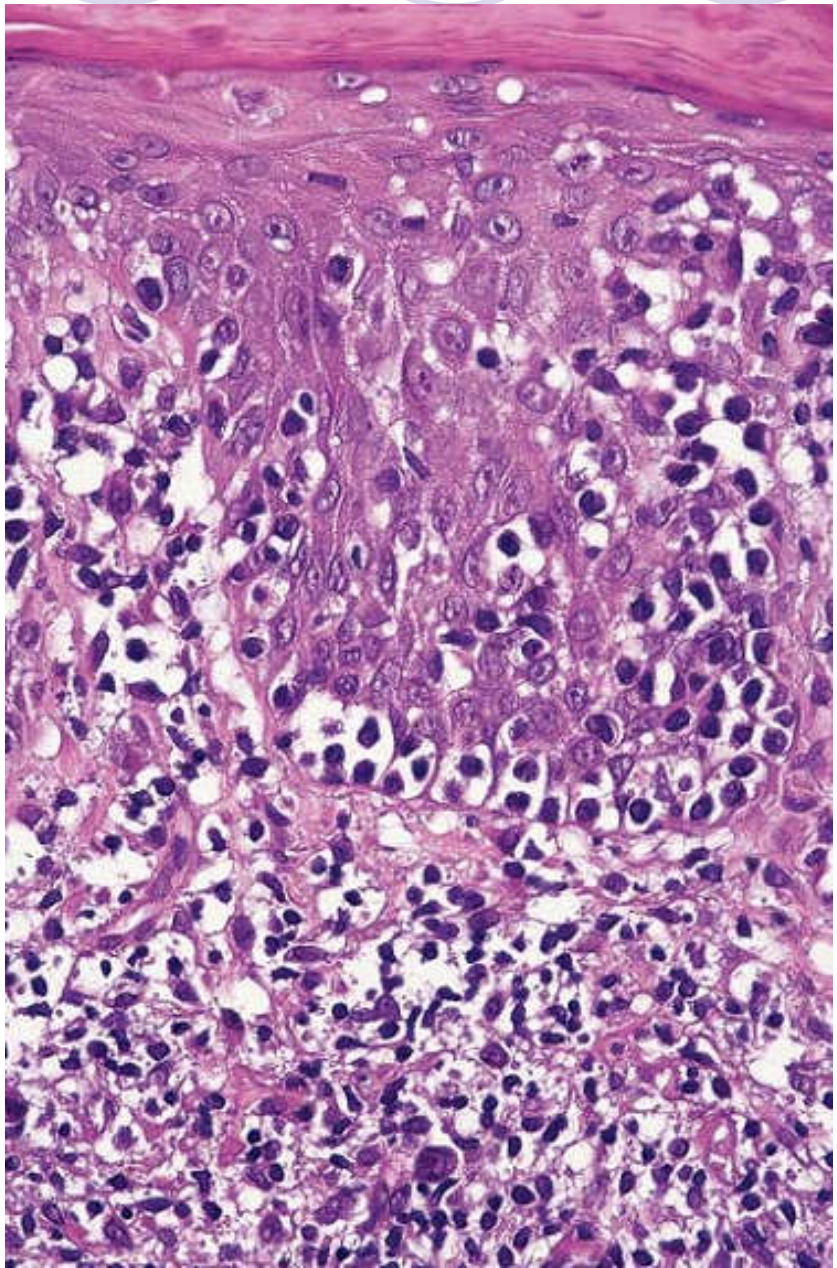
Pagetoid reticulosis

- indolent localized variant of MF
- solitary erythematous scaly or verrucous patch on the distal extremities or acral skin
- rare disease
- very long, persistent and indolent course
- male predominance
- Hx: prominent pagetoid epidermotropism
- DDx tinea, lupus vulgaris, neoplasm, metastasis
- good response to local radiation



Pagetoid reticulosis

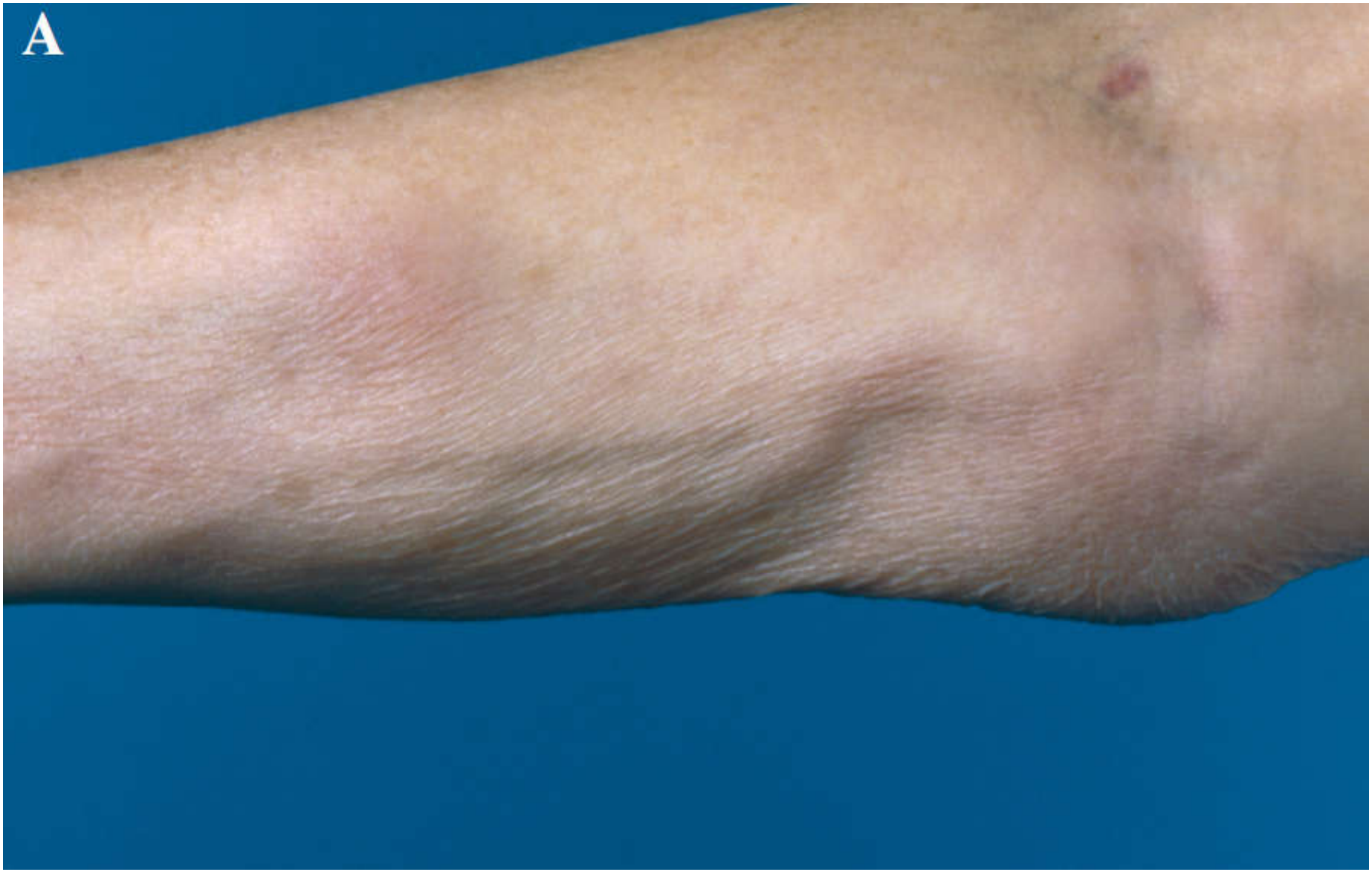
- striking epidermotropism
- numerous atypical mononuclear cells, singly or in clusters
- immunoprofile of lymphocytes: CD4+ or CD8+ or gamma/delta



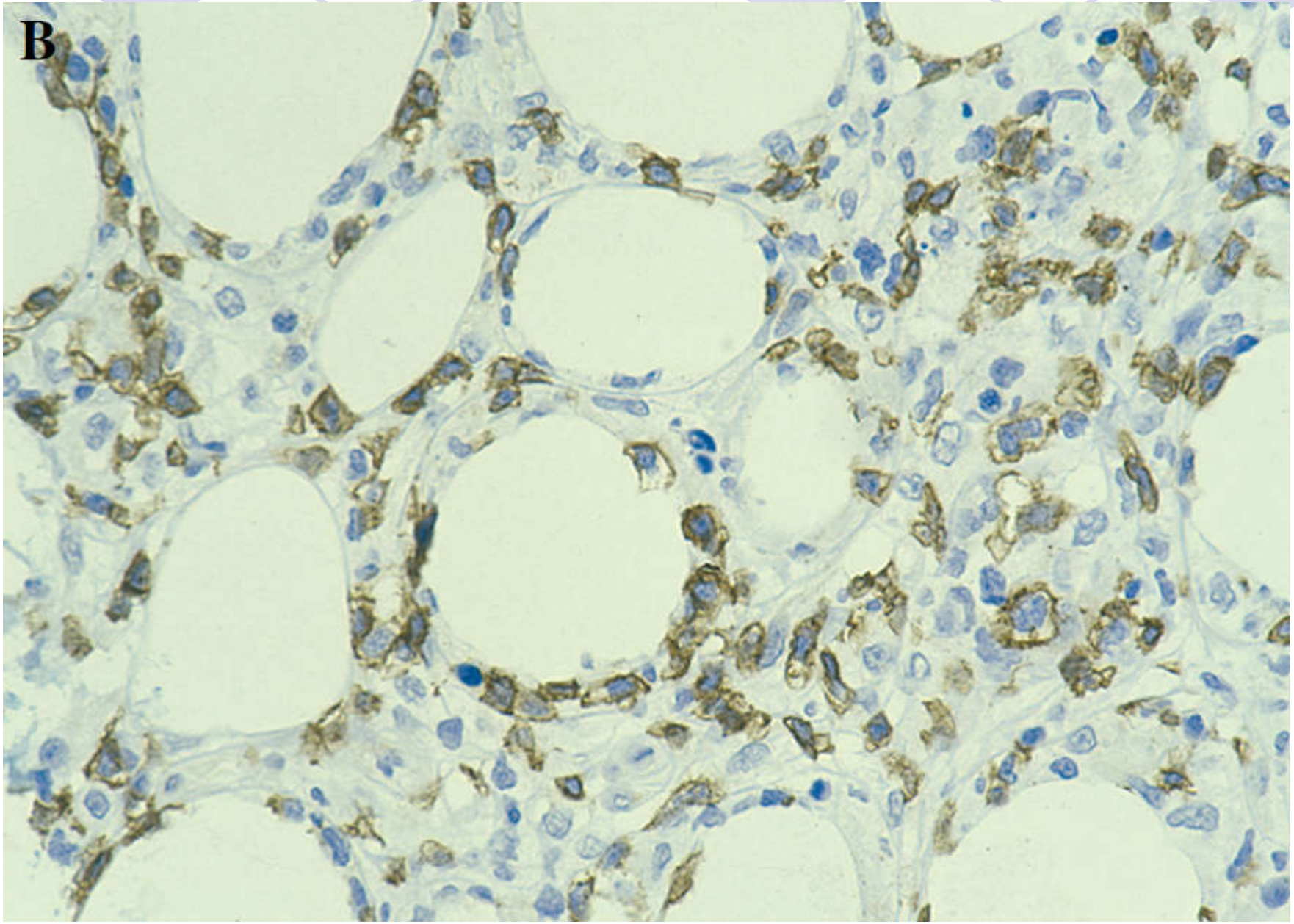
Lymphomas with a good prognosis with survival > 5 years

- mycosis fungoides
- pagetoid reticulosis
- granulomatous slack skin
- primary cutaneous small/moderate sized pleomorphic T-cell lymphoma
- primary cutaneous anaplastic large-cell CD30+ lymphoma (pierwotny chłoniak skórny anaplastyczny z dużych komórek CD30+)
- lymphomatoid papulosis
- subcutaneous panniculitis-like T-cell lymphoma

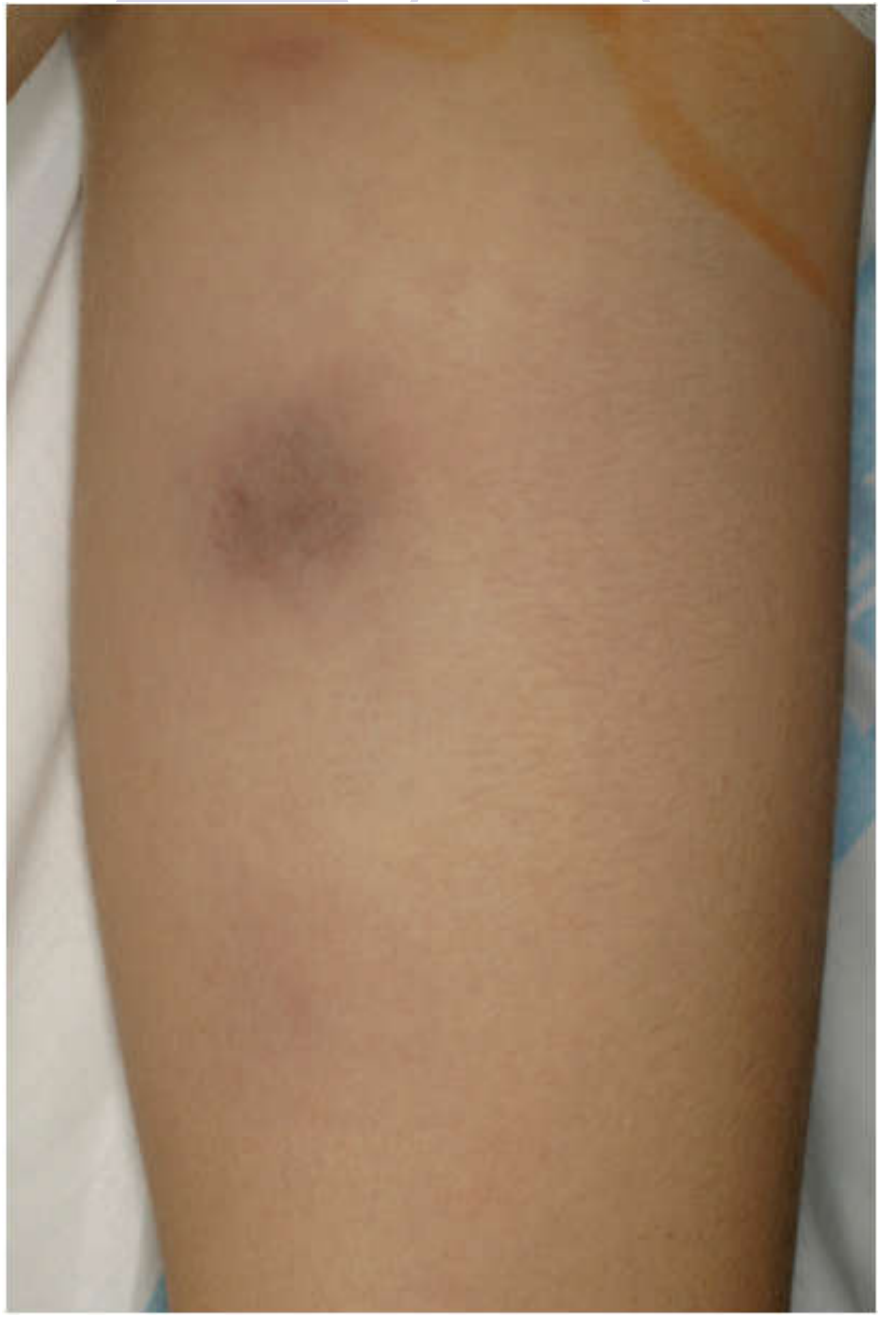
Subcutaneous panniculitis T-cell lymphoma (alpha/beta T-cell phenotype) – clinically nodules in the fat



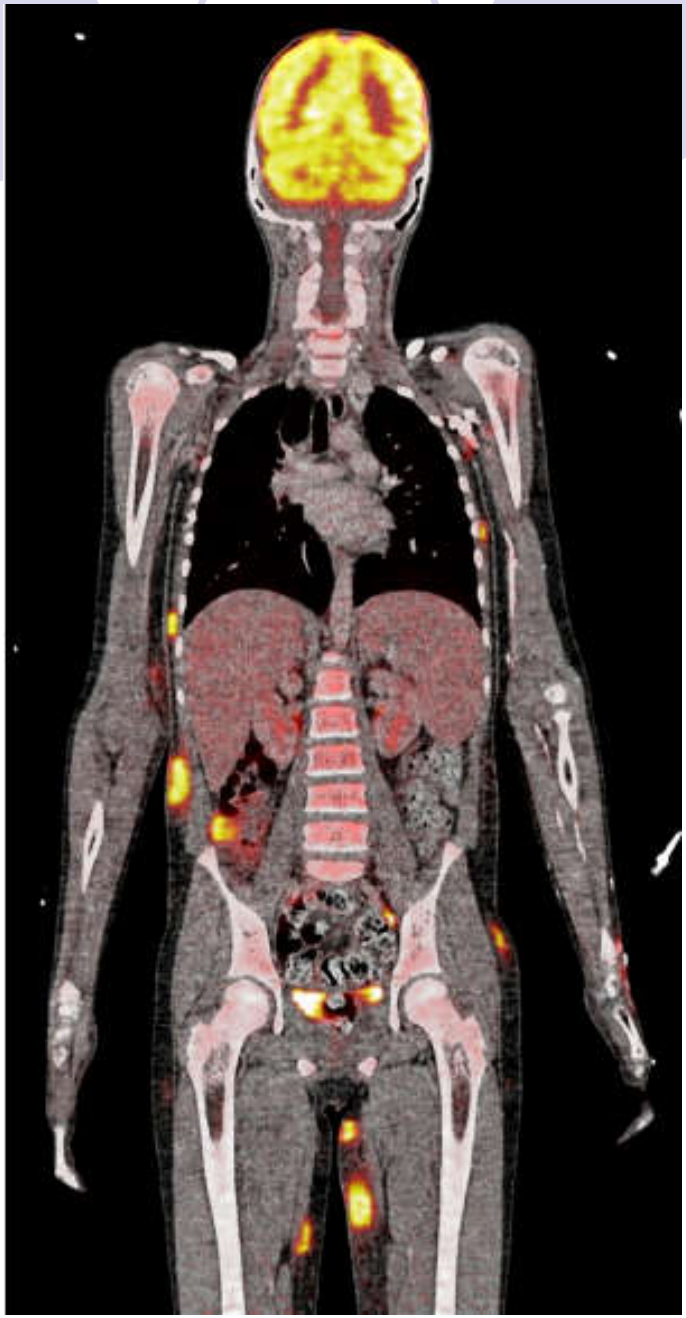
Subcutaneous panniculitis T-cell lymphoma (alpha/beta T-cell phenotype) – monomorphic atypical lymphocytes form a rim around adipocytes



Subcutaneous panniculitis T-cell lymphoma



Nodule like a bruise on the lower leg, present for a year



positron emission tomography reveals other tumors

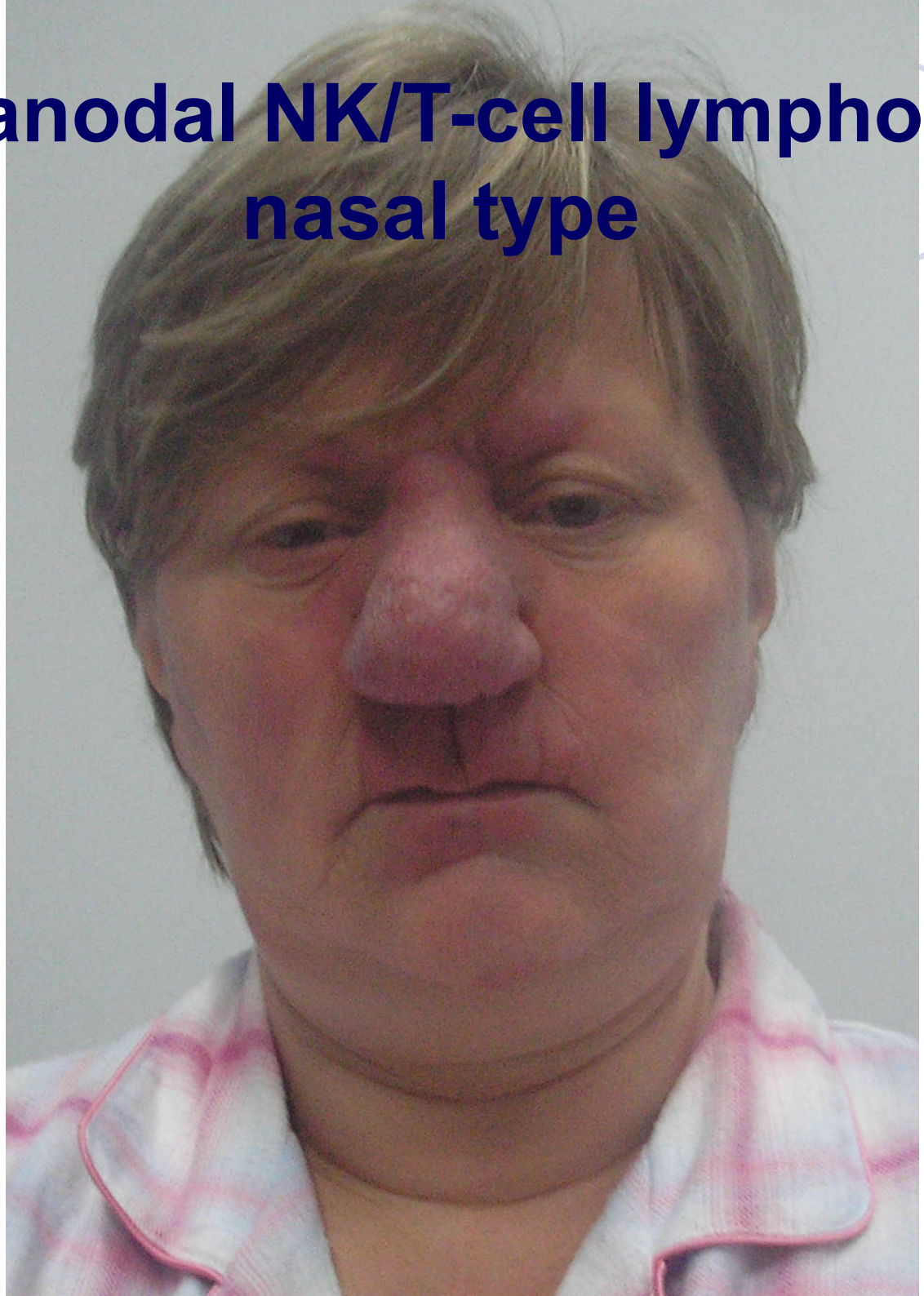
Lymphomas with moderate prognosis (2-5 years of survival)

- Sezary syndrome
- folliculotropic mycosis fungoides
- adult T-cell leukemia/lymphoma (HTLV+)
- primary cutaneous diffuse large B-cell lymphoma, leg type
- primary cutaneous diffuse large B-cell lymphoma, other types

Lymphomas with poor prognosis < 2 years

- extranodal natural killer (NK) T-cell lymphoma, nasal type
- primary cutaneous aggressive epidermotropic CD8+ T-cell lymphoma (provisional)
- primary cutaneous γ/δ T-cell lymphoma
- primary cutaneous intravascular large B-cell lymphoma
- subcutaneous panniculitis-like T-cell lymphoma with hemophagocytosis
- $CD4^+/CD56^+$ hematodermic neoplasm.

Extranodal NK/T-cell lymphoma, nasal type



Parapsoriasis

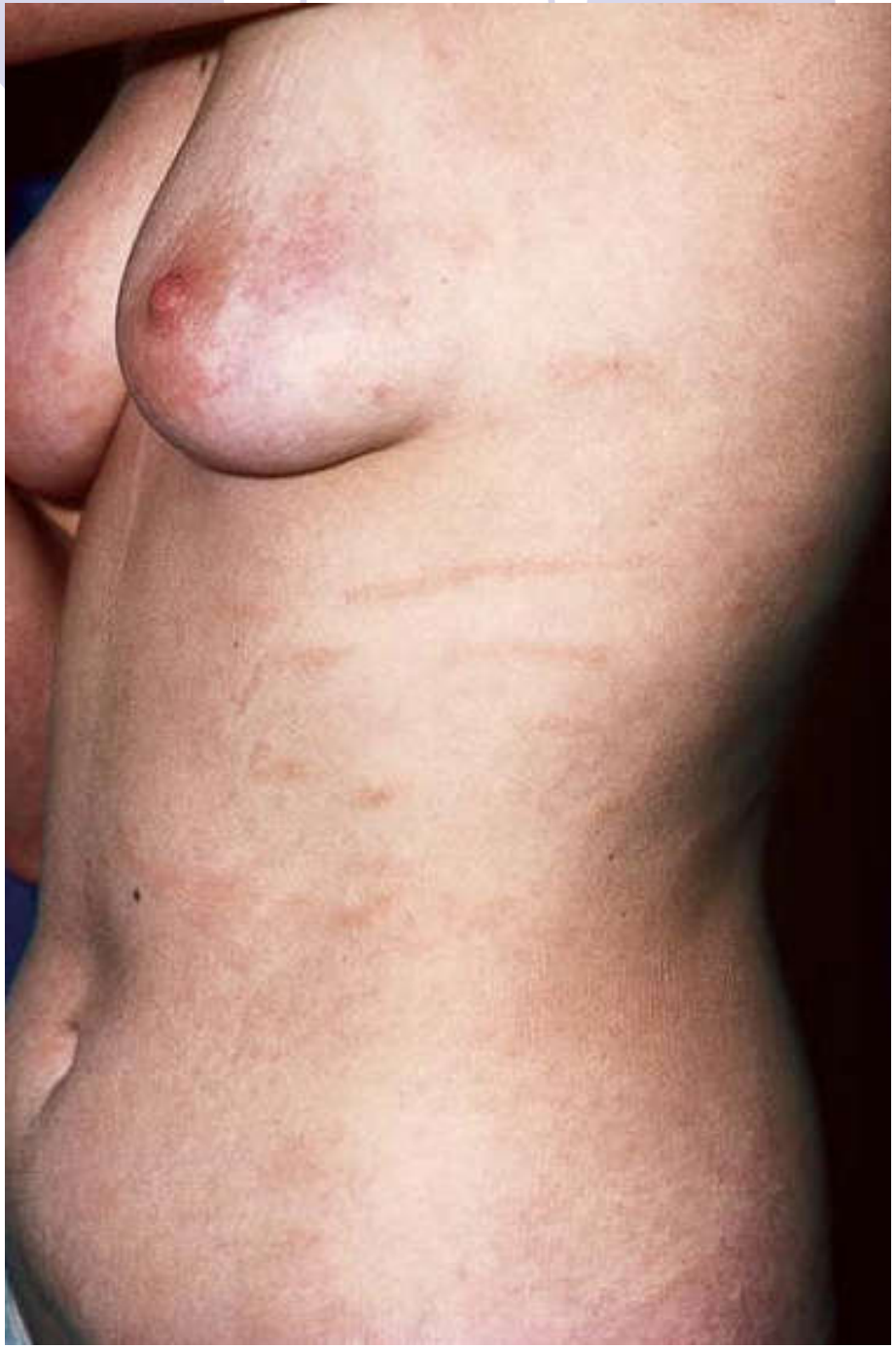
- Is it lymphoma from the beginning with a slow progression or chronic dermatitis stimulating lymphocytes for malignant transformation ?
- parapsoriasis types:

1. Small-plaque parapsoriasis
2. Large-plaque parapsoriasis
3. Poikiloderma atrophicans vasculare

The risk of malignant transformation is high and MF can develop in 20% of cases.

Small-plaque parapsoriasis

- digitiformis, finger-prints
- chronic, well marginated, mildly scaly, slightly erythematous, oval or elongated skin lesions measuring < 4-5cm in diameter
- trunk and proximal extremities in a pityriasis rosea-like pattern
- this form does not progress to lymphoma



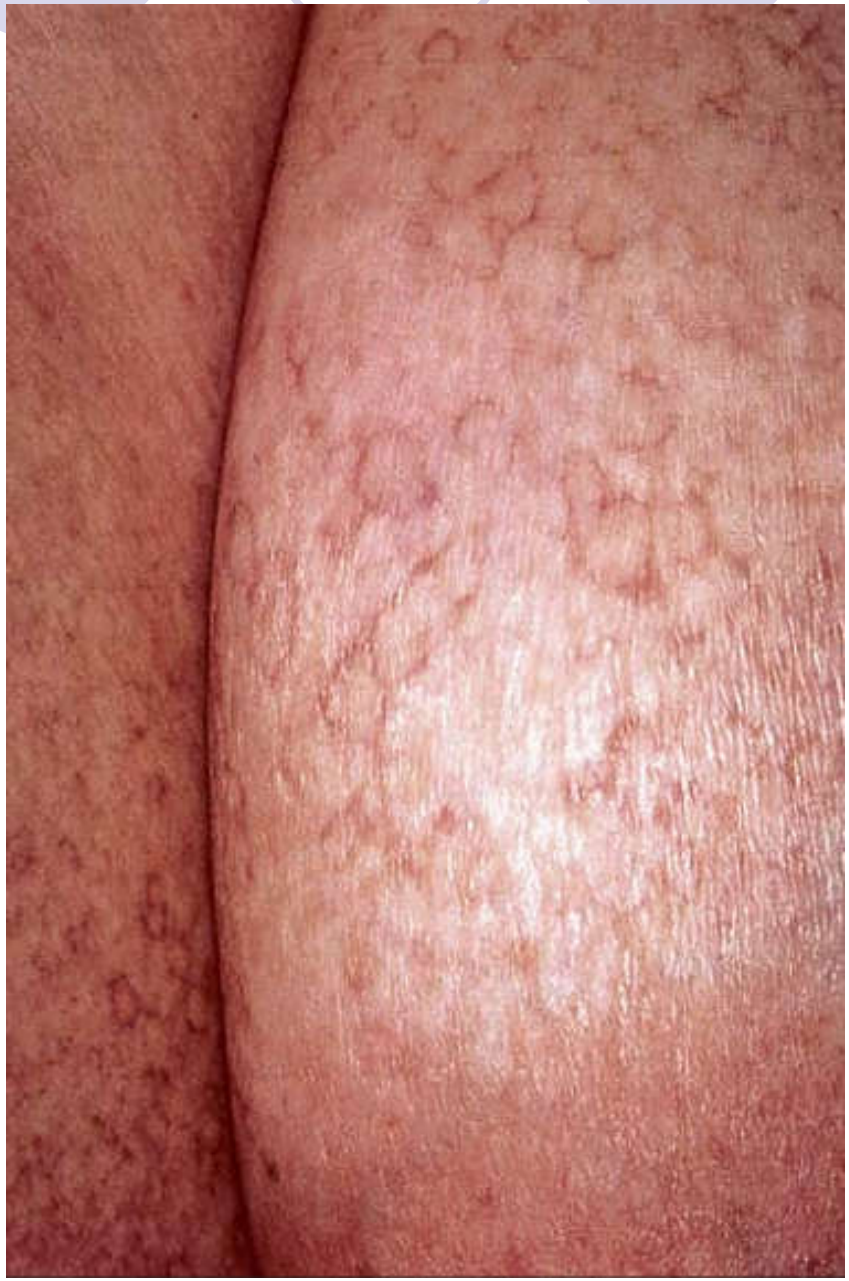
Large-plaque parapsoriasis

- this disease can precede MF development
- patient has to be regularly checked-up
- consider repeated biopsies, every six months
- „status pre-mycoticus” vs mycosis fungoides of an early stage
- UV - therapy (PUVA, NB-UVB, Re-PUVA)
- the disease can be stable for years and never transform into MF
- palm-sized or larger skin lesions located most frequently on the thighs, buttocks, hips, lower abdomen and shoulder girdle
- color of the lesions: pink, red-brown, or salmon
- fine scale on the top
- epidermal atrophy with cigarette-paper wrinkling

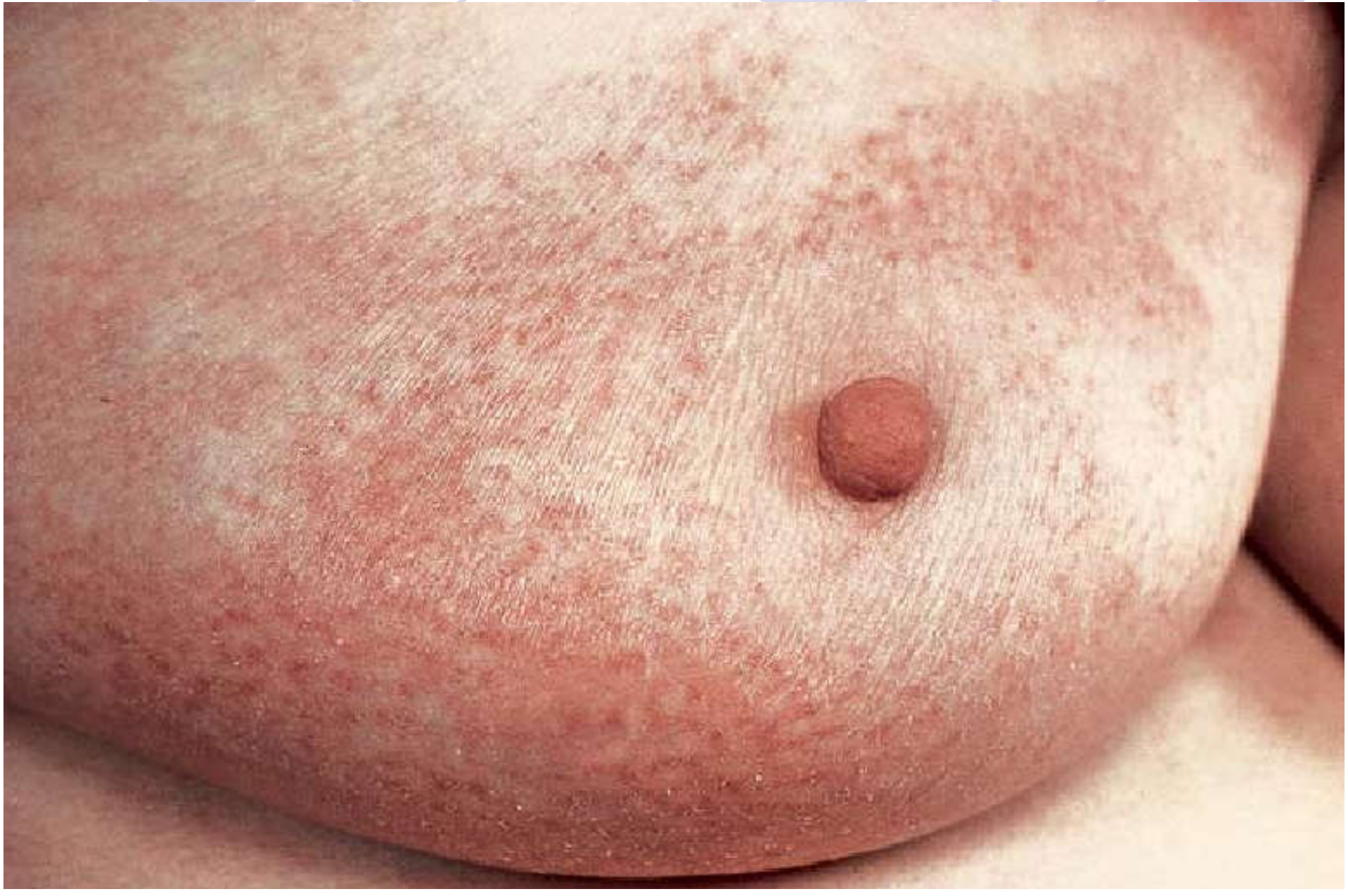
- Pruritus!!! and elevation as indicators of transformation

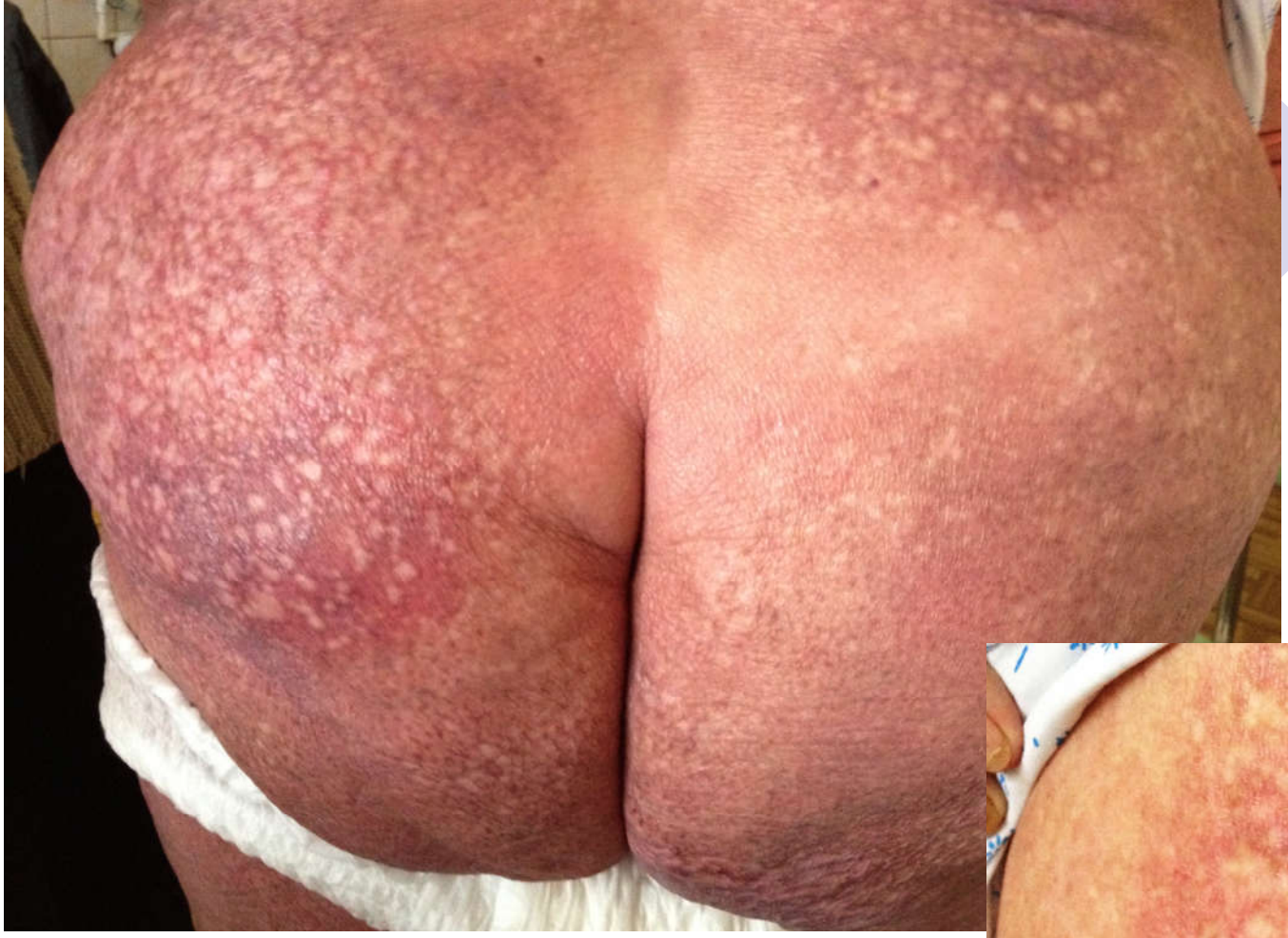
Large plaque parapsoriasis – poikilodermic variant

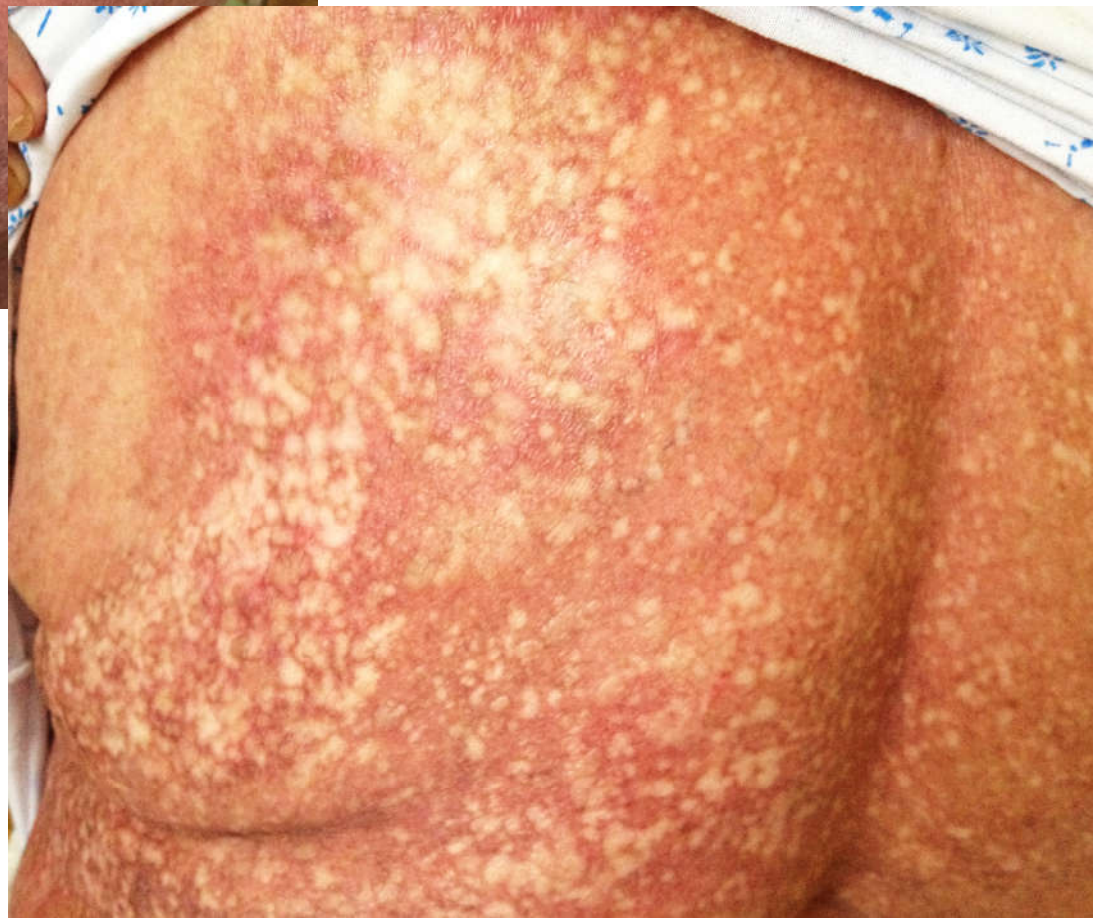
- variegata
- poikilodermia atrophicans vasculare
- predilection for the breast, buttocks, hips, abdomen and major flexures
- atrophy, telangiectasia, hypo- and hyperpigmentation with erythema
- this is a premalignant type of MF
- pruritus is a symptom of malignant transformation !!!
- dermatological treatment of choice



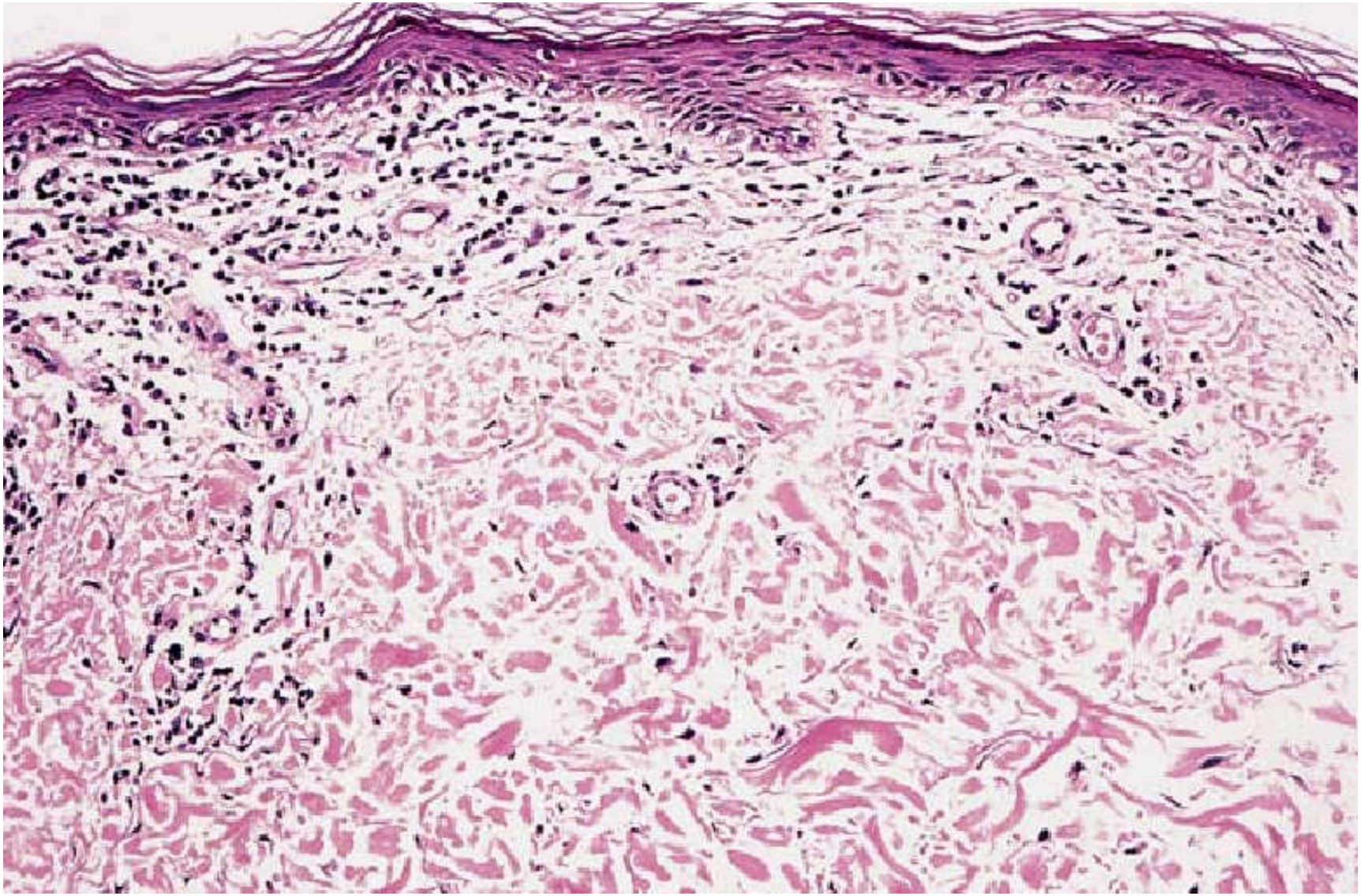
Poikiloderma atrophicans vasculare – variant of large plaque parapsoriasis







Poikiloderma atrophicans vasculare



Sezary syndrome

Three symptoms – classic triad

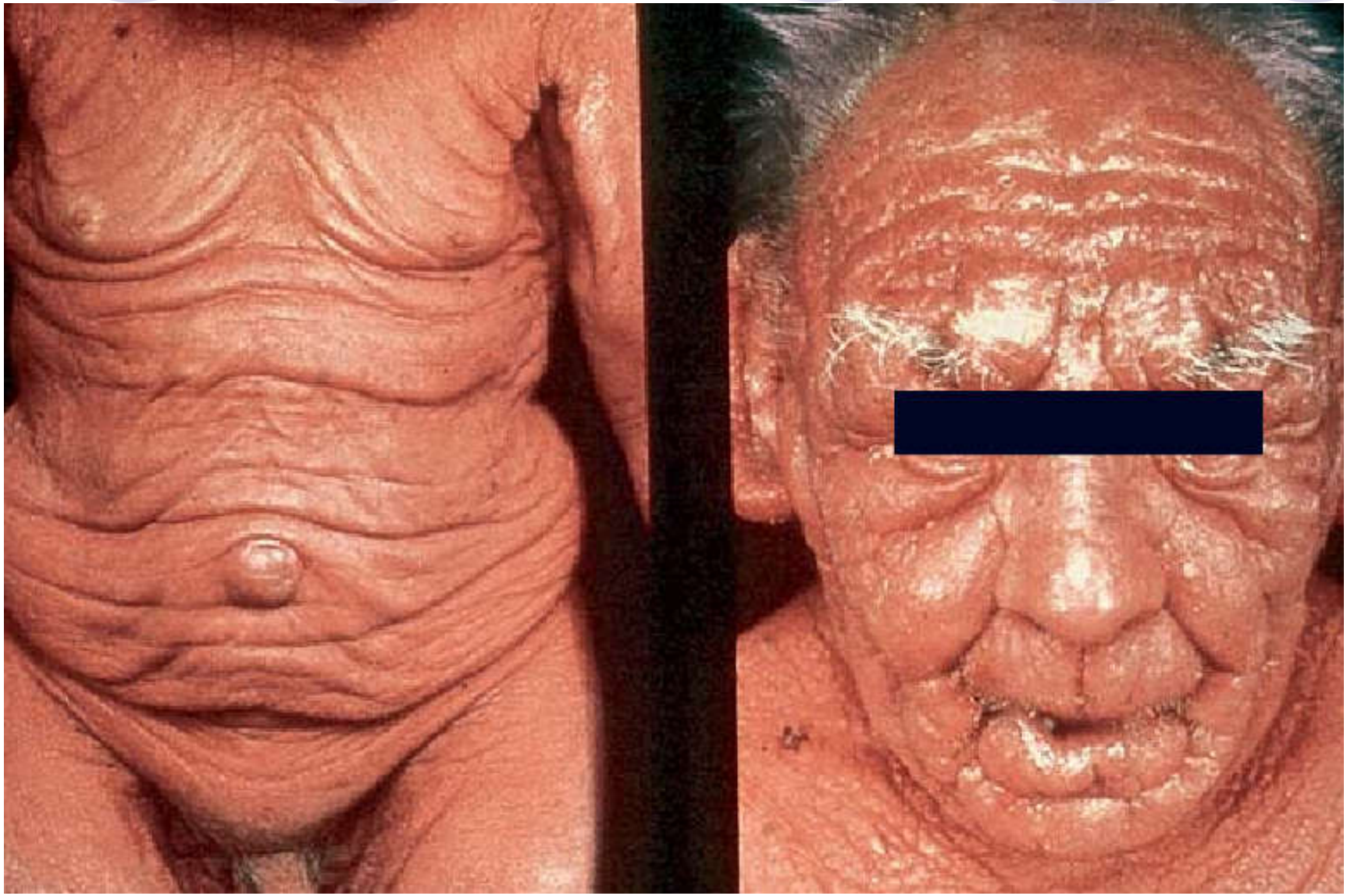
Erythroderma

Lymphadenopathy

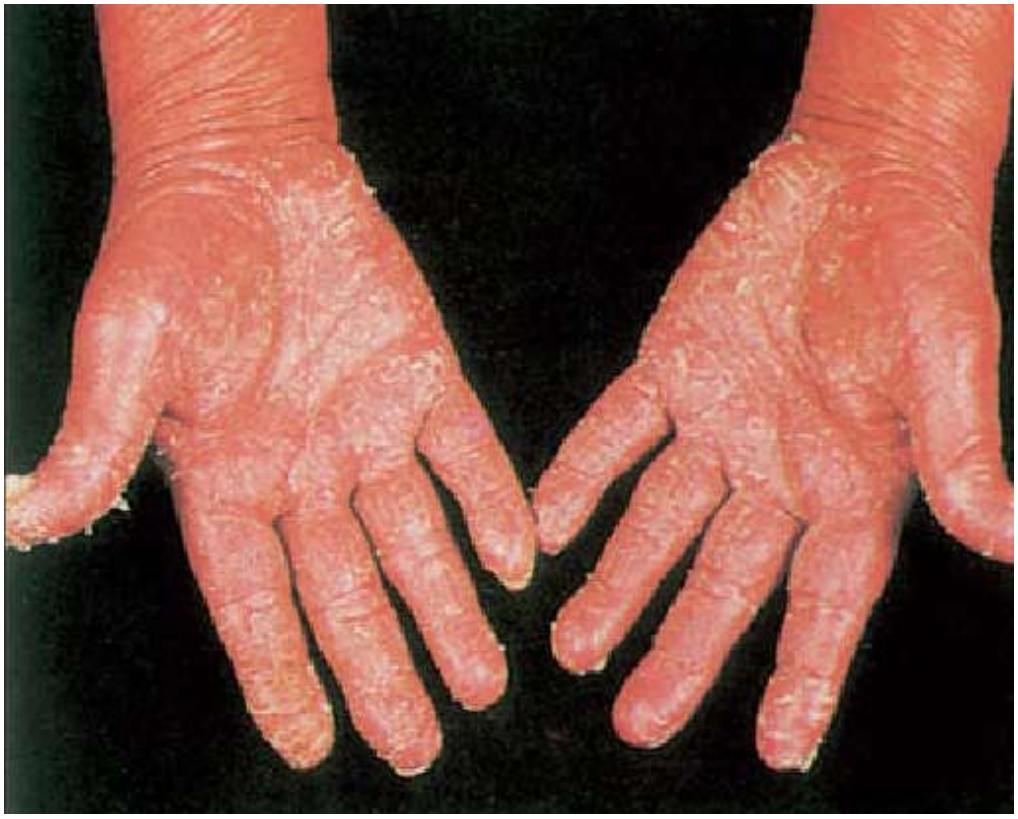
Atypical lymphocytes circulating in the blood

This is an erythrodermic leukemic manifestation of T-cell lymphoma whith worse prognosis than MF.
5-yr survival – 10-20%

Sezary syndrome



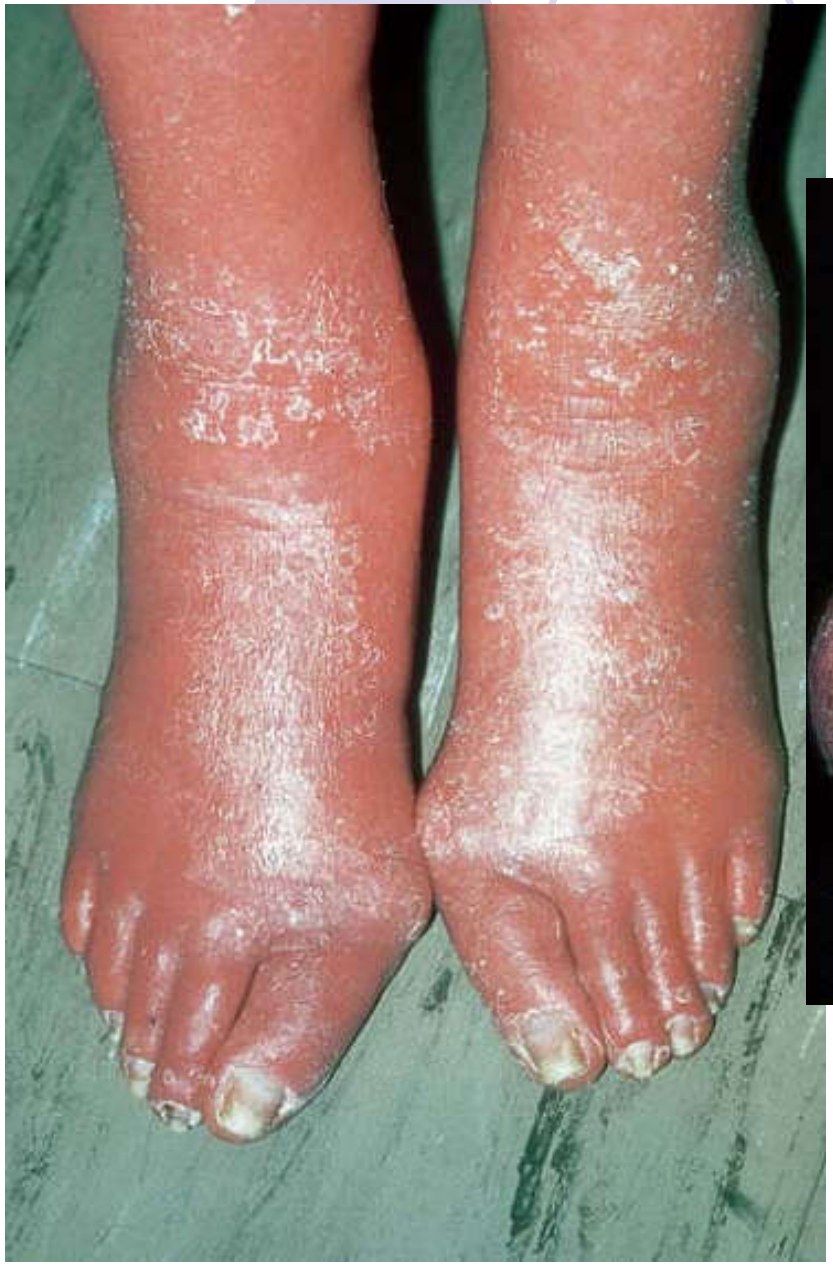
Sezary syndrome skin findings

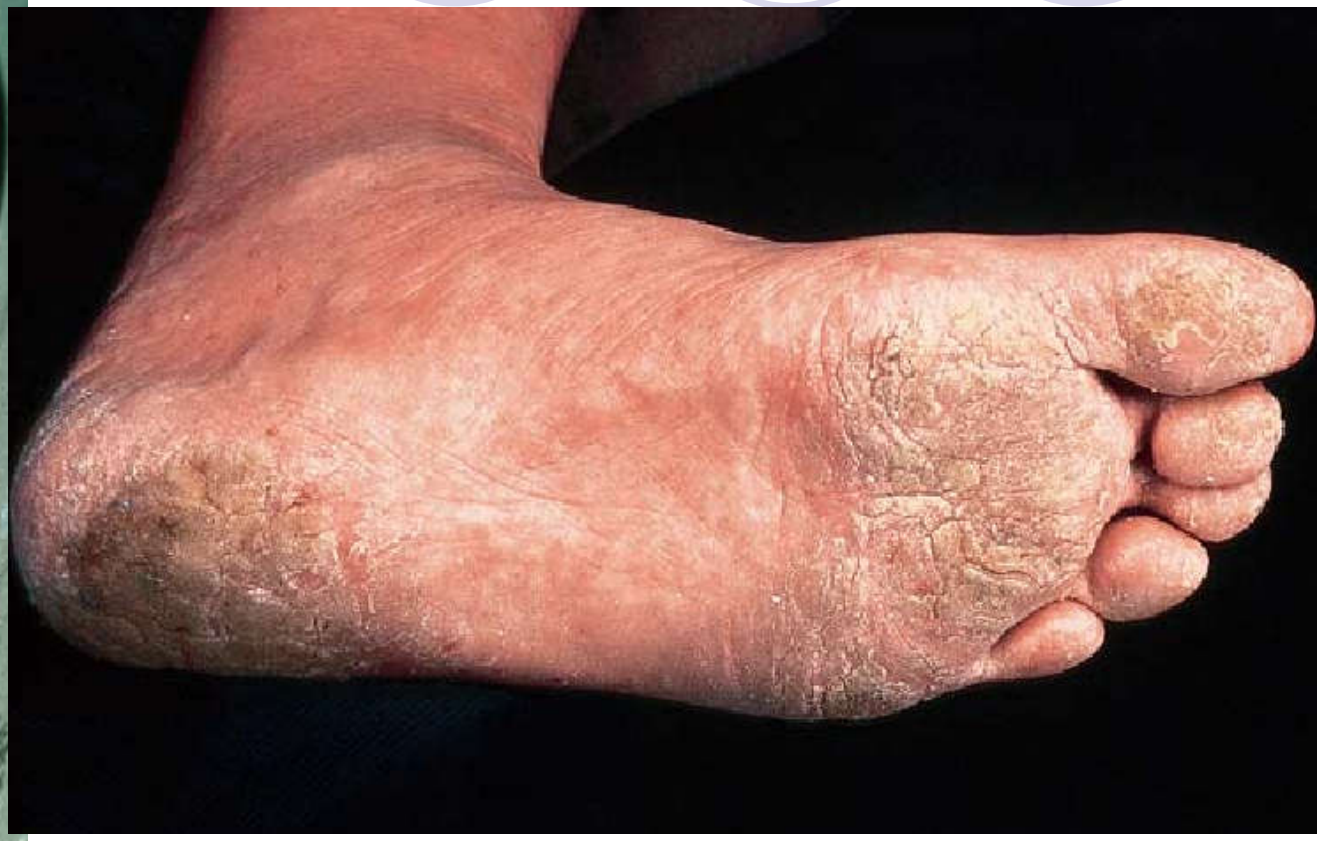


- classical triad

1. Erythroderma

- severe pruritus
- ectropion
- nail dystrophy
- peripheral edema
- alopecia
- keratoderma of the palms and soles





Sezary syndrome

Hematological findings

- circulating blood

- >1000/ml atypical, big lymphocytes with cerebriform nuclei
- Increased number of CD4+
- Increased ratio of CD4+/CD8+ > 10
- Lost markers of CD5; CD7; CD26

- clonality of T lymphocytes (PCR confirmed rearrangement)

- Skin - erythroderma
- Lymphadenopathy

Sezary syndrome treatment

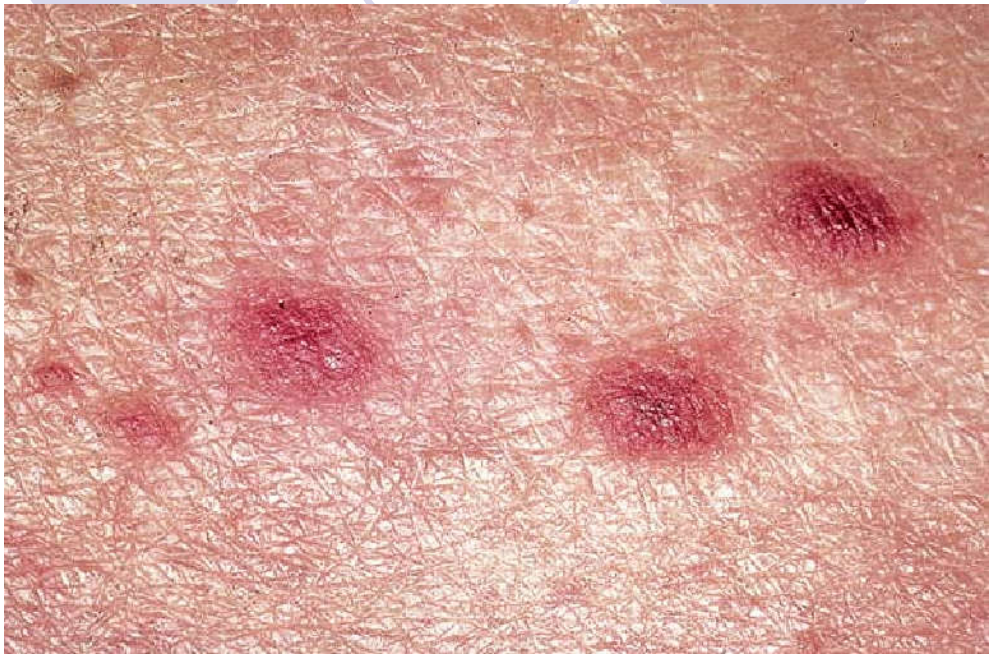
- Extracorporeal photophoresis (FDA-approved)
- INF-alfa
- Phototherapy: PUVA, Re-PUVA, NB-UVB
- Oral retinoids and rexinoids (bexaroten, acitretin)
- Methotrexate 5-75 mg/week
- Chlorambucil
- Electron-beam therapy
- Chemotherapy
- Radiotherapy

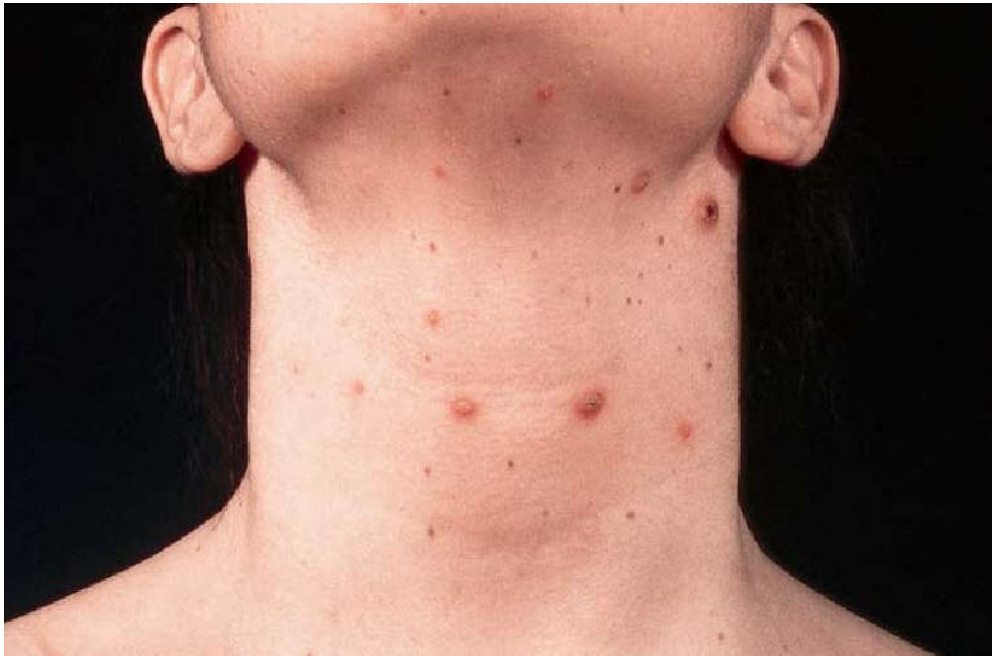
Primary cutaneous CD30+ large cell lymphoma

- Lymphomatoid papulosis
- Anaplastic large T cell lymphoma
- Borderline cases

Lymphomatoid papulosis

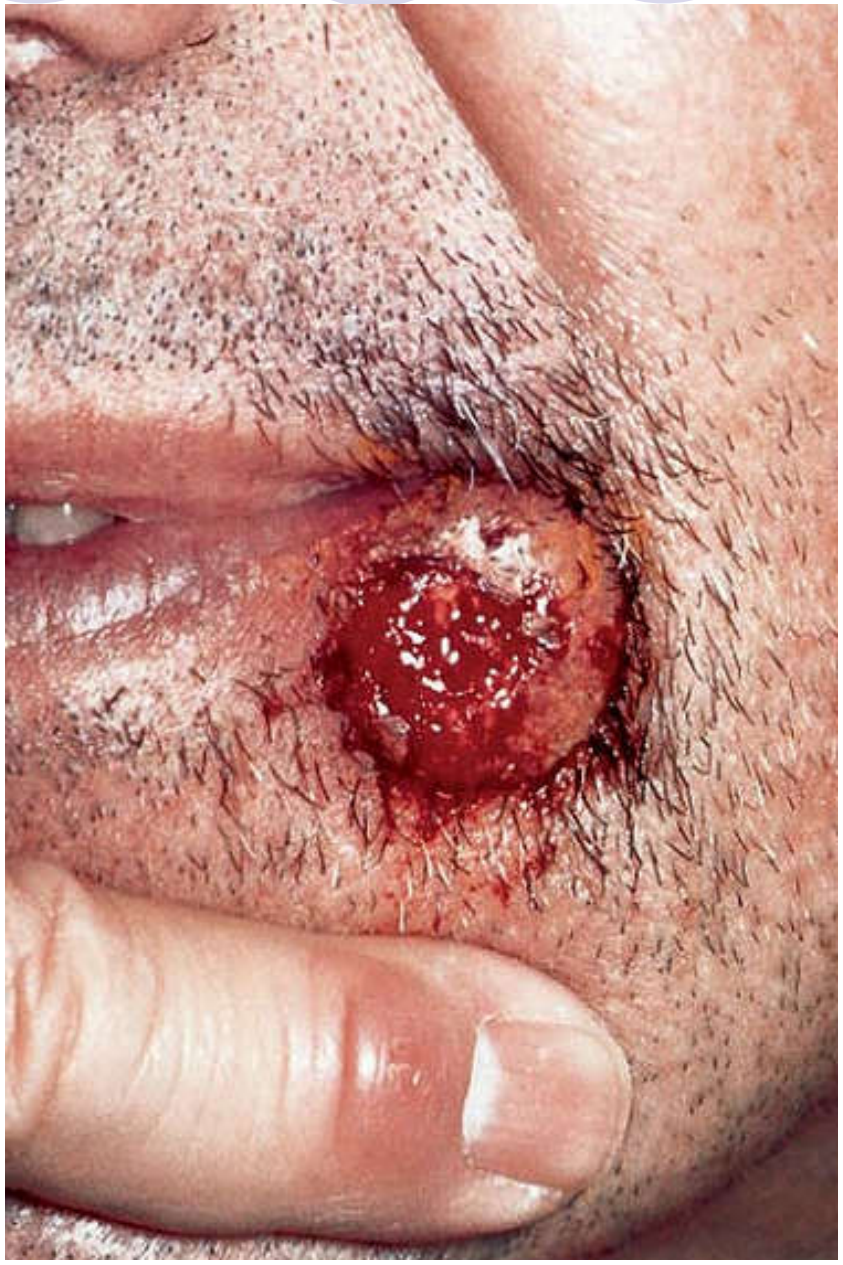
- male predilection (2:1)
- wide range of age group can be affected
- patient develops crops of erythematous, asymptomatic dermal papules
- which become in 3-4 weeks hemorrhagic and necrotic
- then heal with atrophic scars
- trunk and limbs are mainly affected
- the main DDx is PLEVA





Anaplastic large CD30+ T cell lymphoma

- most common in the 5-7th decade
- solitary erythematous or violaceous nodule/tumor appears restricted to a single region
- males more often affected than females
- 5-yr survival ranges from 91-96%



Anaplastic large T cell lymphoma